ARCHIVES OF DISEASE IN CHILDHOOD.

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ON THE ÆTIOLOGY AND TREATMENT OF PINK DISEASE

BY

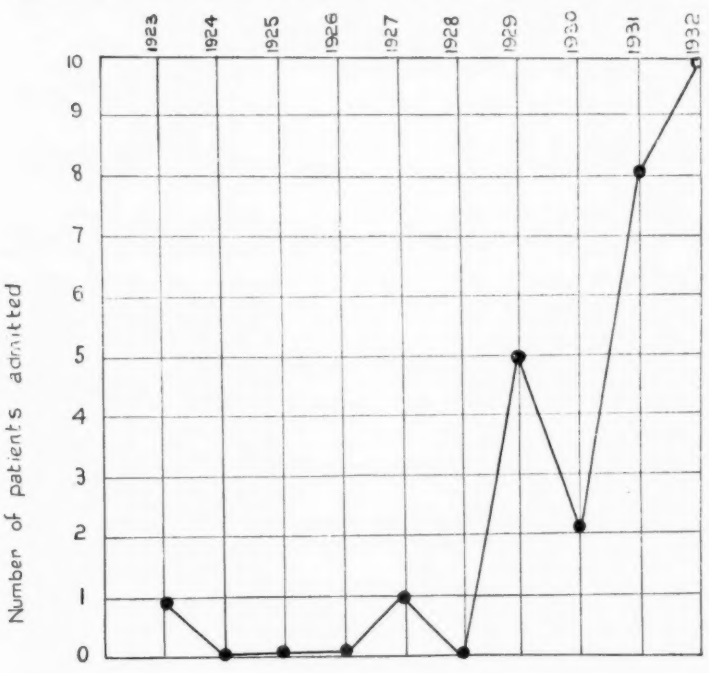
J. VERNON BRAITHWAITE, M.D., M.R.C.P.
(From the Children's Hospital, Leicester Royal Infirmary.)

Pink disease, first described by Swift[1] in Australia in 1914, was brought to the notice of the profession in this country by Thursfield, Paterson, and Greenfield[2, 3] in 1922 and 1923. Since then a large number of cases have been reported and many excellent clinical descriptions have been given. Concerning the ætiology and treatment, however, there is still no certain knowledge, and different observers have reported conflicting results. The fact that most cases tend to recover slowly in hospital is no doubt partly the cause of this.

Incidence.—The disease appears to be getting more common, at any rate in the Midlands. Parsons[4] in 1930 recorded an increasing incidence in Birmingham; whereas in 1920 only 2 cases were on record, there were 18 in 1929. The numbers admitted to the Children's Hospital of the Leicester Royal Infirmary since 1923 are shown in Chart I. Of the 27 cases on which this paper is based, 25 have occurred in the last four years.

CHART I.

ANNUAL INCIDENCE IN THE CHILDREN'S HOSPITAL, LEICESTER.



The great increase in the number of admissions during the last two years may be in part due to practitioners becoming familiar with the disease.

Symptoms.—The symptoms and signs of pink disease are now so well known that a detailed account of them is unnecessary. The cardinal symptoms are erythrœdema, a polymorphic rash followed by desquamation, marked anorexia, muscular hypotonia, mental depression, photophobia, and sweating. The condition can be diagnosed at a glance. One sign has been constantly observed in this series which is not mentioned elsewhere, namely, the rapid eruption of teeth. Falling out of the teeth, which is said to be most typical of the disease, only occurred in one of these patients, and alopecia was not marked. In other ways the symptomatology in the present series of cases agreed closely with that given in the literature.

Ætiological factors.

Sex.—Most observers record a preponderance of males. In this series the sexes were equal, 14 girls and 13 boys.

Age at onset.—This is difficult to ascertain with accuracy, as the onset is so insidious. Vague symptoms of nasal catarrh gradually develop into the complete clinical picture. As far as could be determined the age at onset varied from 4 to 22 months, averaging 9 months.

Diet.—This in our cases was always good. Eighteen patients had been wholly or partially breast fed, and the diet of the others was well supplied with vitamins.

Geographical distribution.—The disease was first described in Australia, and cases have since been reported from America, New Zealand, and Switzerland, as well as from this country. It should be noted that the cases from abroad have all occurred in particularly sunny countries.

When the local geographical distribution is considered it is seen that pink disease is an illness of rural rather than of urban districts. Twenty of the 27 cases under consideration (74 per cent.) came from suburban or country homes; whereas of the last 500 children admitted into the Children's Hospital only 58 per cent. came from the suburbs or country.

Number in family.—Eight out of 22 of these patients were only children. The average number of children in the family was 2·7.

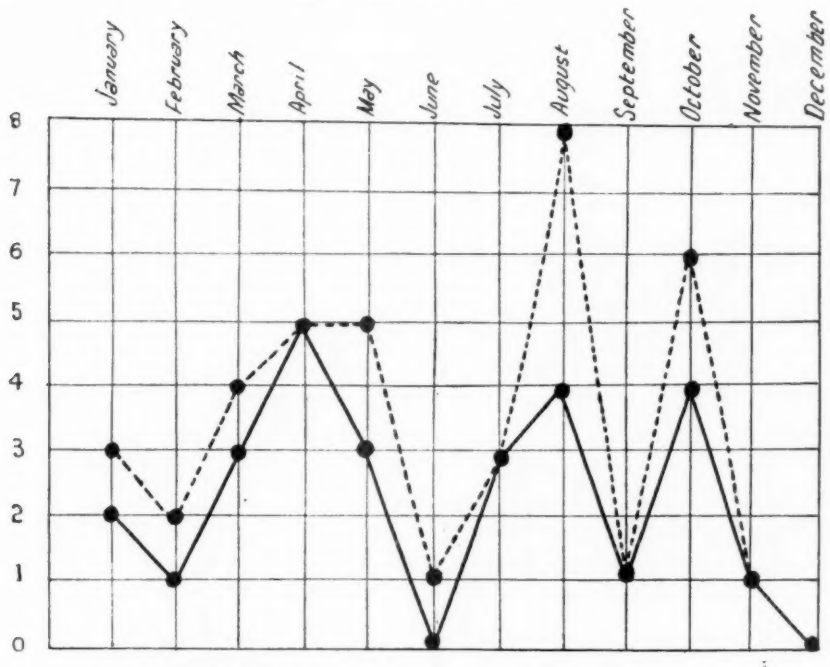
It is concluded, therefore, that pink disease occurs chiefly in well cared-for children in good surroundings.

Seasonal incidence.—Previous accounts do not show any marked seasonal variations. The majority of these cases were admitted either in the early summer or autumn, while only 4 were admitted between the months of October and March. If the cases reported by Paterson and Greenfield[3], and Wyllie and Stern[10] (in which the date of admission is given) are added

to our own, making a series of 39 patients from this country, the biennial rise becomes more pronounced. The maximum number of admissions is in August. It is fully realized that there is usually history of one or two months' illness before the child is admitted, but it is at this time that the child becomes so much worse that hospital treatment is sought. It is suggested that the vernal rise is due to recent prevalence of acute respiratory catarrh, and that the autumnal increase is due to the continued effect of increased daylight.

CHART II.

SEASONAL INCIDENCE.



Present series ————————

Present series with Paterson and Greenfield's, and Wyllie and Stern's cases - - - - - - - - - - - - - - - -

Prodromal infections.—Some form of acute respiratory catarrh invariably precedes or accompanies the onset of the disease. Byfield[5] in his classical account found respiratory infection constantly present. In 12 of the cases of the present series the mother definitely attributed the illness to a severe cold; in 1 patient it followed tonsillitis, in 1 measles, and in 1 broncho-pneumonia. Running of the eyes and nose was invariably present.

Summary of ætiological factors.—The foregoing facts suggest that pink disease is due to an abnormal reaction to daylight in a child that has recently suffered from an acute infection of the respiratory tract.

In this connexion it is interesting to note the experiments of L. J. Harris[6] on hypervitaminosis D in the rat. It was found that a moderate excess of vitamin D produces a greatly increased net absorption of calcium and

phosphorus, a tendency to hypercalcæmia and hyperphosphatæmia, and excessive formation of densely calcified new bone. Similar changes occur in the teeth, the cement becoming over-calcified and a remarkable overgrowth of cementoid forming, which may become ankylosed to the alveolar bone; abnormal new deposits of dentine are also laid down; lime salts are extensively deposited in the soft tissues. If maximal toxic doses of the vitamin are given, however, the animal becomes very ill with loss of appetite and a breakdown in the gut function, and the changes described as the result of increased calcium absorption are not observed. In children Hess and Lewis[7] had obtained very similar results. They found that irradiated ergosterol in doses of 2·5–5 mgrm. not only cured rickets, but caused hypercalcæmia and hyperphosphatæmia. Beyond causing eburnation of the healed bones, this was not associated with any marked clinical effects. In 2 of their cases, however, the excess of blood calcium was accompanied by curious symptoms. There was moderate fever, marked drowsiness, and a peculiar mental condition. The electrical reactions were found to be sluggish. Albumin and casts appeared in the urine. Although the blood calcium rose considerably, the phosphorus remained normal. All these symptoms and signs have been repeatedly observed in pink disease.

The blood in pink disease.

Blood calcium and phosphorus.—Acting on the above hypothesis, that pink disease is essentially an abnormal reaction to light in an infected child, it was decided to estimate the blood calcium in patients suffering from this illness. This was done in 18 cases, and the plasma phosphorus was estimated in 4 cases. The results are given in Table 1.

TABLE 1.

CALCIUM AND PHOSPHORUS ESTIMATIONS IN PINK DISEASE.

Case	Calcium mgrm. per 100 c.cm. serum	Phosphorus mgrm. per 100 c.cm. plasma
N. A.	11·02	
J. T.	12·3	4·6
J. S.	10·6	
A. D.	11·9	
K. L.	11·2	
D. G.	11·6	4·9
K. M.	14·2	
B. P.	11·7	
T. W.	11·0	
E. G.	12·3	
R. D.	11·3	4·1*
N. J.	11·7	
J. T. (a)	11·3	
M. T.	11·5	
A. T.	12·1	
P. C.	10·5	4·6
G. W.	10·9	
K. M. (a)	11·2	

* After treatment by intraperitoneal citrate.

It will be seen from Table 1 that the blood calcium is slightly but definitely raised in most cases. This may well be the cause of some of the symptoms, e.g., muscular hypotonia, mental depression, and the rapid cutting of teeth. In the cases in which the phosphorus was estimated this does not show any corresponding rise. These results are similar to those obtained by Hess and Lewis[7] in hypervitaminosis D.

Blood counts.—The cellular elements of the blood were found to be almost constantly increased. Previous observers have recorded the constant occurrence of leucocytosis. In my experience a marked increase in the number of red blood cells and a rise in the percentage of hæmoglobin were almost equally constant (Table 2). It is suggested that the degree of leucocytosis is dependent on the activity of the respiratory infection.

TABLE 2.

BLOOD COUNTS IN PINK DISEASE.

Case	Red cell count	Percentage of hæmoglobin	White cell count	Percentage of polymorph. cells
N. A.	5,250,000	98	13,000	34
J. T.	5,600,000	110	16,000	64
J. S.	6,166,000	93	7,187	21
A. D.	6,066,640	102	10,937	48
K. L.	4,420,000	75	14,000	53
D. G.	4,833,000	70	18,437	64
K. M.	6,800,000	97	15,000	80
B. P.	5,633,000	89	9,687	41
T. W.	5,466,000	92	13,437	60
E. G.	6,133,000	100	10,396	36
R. D.	5,502,000	85	23,437	68
N. J.	4,634,000	93	8,432	49
J. T. (a)	5,716,000	103	9,060	44
N. T.	6,606,000	120	28,124	29
A. T.	5,450,000	100	20,937	32
P. C.	6,017,000	90	14,062	73
G. W.	6,416,000	110	19,062	46
K. M. (a)	5,833,000	100	9,375	

It is seen that the increase in the amount of hæmoglobin is not always in proportion with the increase in red cells. The leucocytosis is very variable, and there is only an occasional increase in the percentage of polymorphonuclear cells.

Sedimentation rate.—This was estimated in 11 patients with very varied results (Table 3). Six showed a very rapid sedimentation rate; 4 of these had over 100 per cent. hæmoglobin. On the other hand 2 patients each had 100 per cent. hæmoglobin but no increase in sedimentation rate. A rapid sedimentation is usually held to indicate a high serum protein, but it is conceivable that it may be due to smallness of the red cells with a normal or increased specific gravity. Further work is required in this and other

directions concerning the physics and chemistry of the blood in pink disease. It may be mentioned, however, that halometric readings suggest that the red cells are small in this affection.

TABLE 3.

Case	Sedimentation rate (mm. per hour)
J. T.	16·25
A. D.	16·25
D. G.	11·25
B. P.	1·125
E. G.	3·75
R. D.	4·875
N. J.	13·0
J. T. (a)	16·25
M. T.	21·5
P. C.	4·75
K. M. (a)	5·25

Treatment.

Pink disease as a rule tends to recovery in hospital. It is my belief that this is due to the fact that the patients are kept indoors there, usually in the middle of a large city, and are thus protected from many of the rays of normal sunlight. But whatever the reason, it has led to several conflicting claims for specific treatment.

Many of the manifestations of the malady suggest a deficiency disease allied to beri-beri or pellagra. There is a good deal of evidence against such an hypothesis: e.g., the varied diet of the great majority of the patients, the high percentage of breast-fed babies of normal mothers, and the occurrence of pink disease in England where vitamin-B deficiency, at any rate to severe degree, is uncommon. Nevertheless, treatment by a diet rich in vitamin B is popular, and good results have been reported from it.

In 1927 Boas[8] produced a curious deficiency disease in young rats by feeding them on a diet adequate in every respect save that the sole source of protein was dried egg-white. The egg-white had to be dessicated before symptoms could be produced, and coagulation by boiling previous to dessication destroyed its harmful effect. Potato starch, egg yolk, and milk among many other substances, protected the animals. The affected rats developed a skin eruption, alopecia, blepharitis, a musty smell and loss of weight. Later they showed skin hæmorrhages and spasticity, and assumed a crouching attitude. Marshall Findlay and Stern[9] repeated the experiments of Boas and confirmed her results. They also found that the disease could be produced in suckling rats by feeding the mothers on a deficient diet. In their opinion this syndrome in the rat is the equivalent of pink disease in children. The terminal symptoms of purpura and spasticity are very different from anything observed in pink disease, but there was a certain amount of support for their hypothesis from post-mortem appearances. The most striking thing about their work was their discovery that raw liver caused all symptoms to disappear rapidly. In 1931 Wyllie and Stern[10]

published the results of feeding 5 patients suffering from pink disease with raw liver. Four of the 5 did well, being practically cured in from 1 to 6 weeks. The remaining child was treated for 3 months at home, but he showed no improvement until he was taken into hospital, when he recovered in a fortnight.

Bruton Sweet[11] treated 17 patients with ultra-violet light from a mercury-vapour lamp. He found that when treatment was given at three-day intervals the condition was relieved in about 4 weeks.

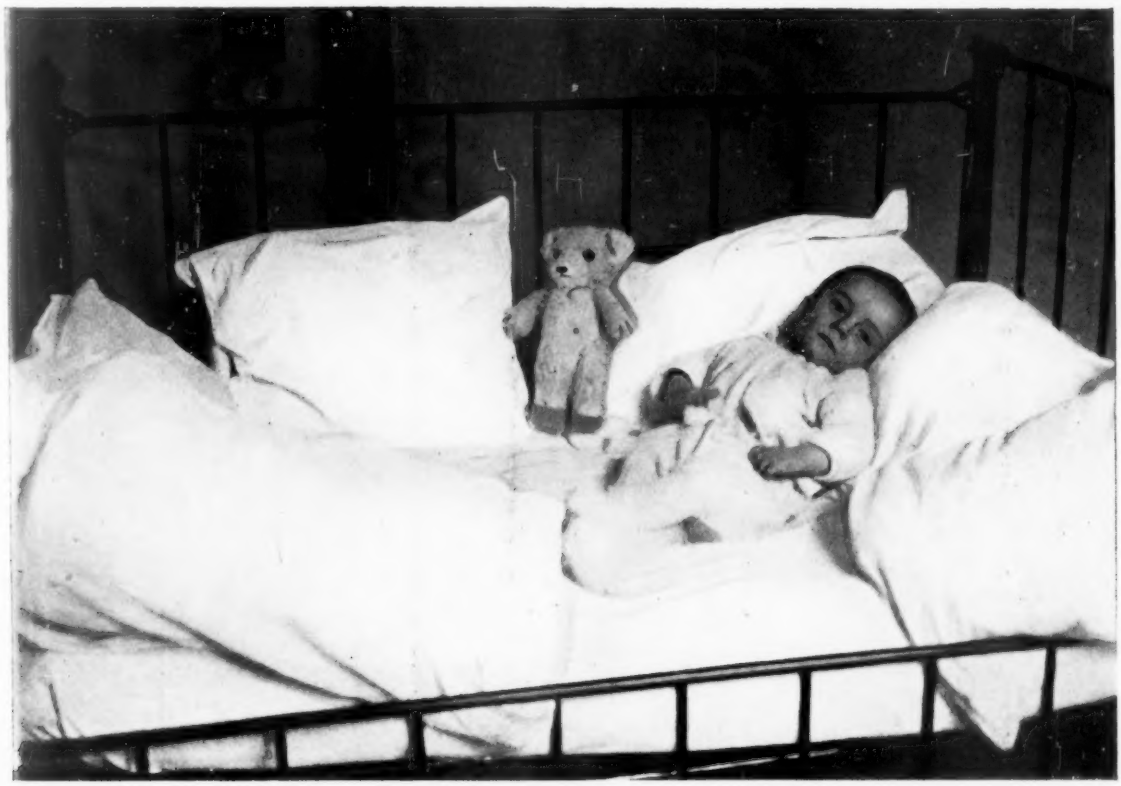


FIG. 1.—Showing the arrangement of the cot.

General measures.—In the treatment of the present series it was found that the patients were more comfortable if they were allowed to assume any position they liked on the bed, uncovered by bed-clothes. They were kept warm by wearing woolly suits which could not be removed by the patient, both hands and feet covered. The sides of the cots had to be protected by numerous pillows (Fig. 1), otherwise the children, especially when they began to recover, tried to sit up and then fell over and hurt themselves on the bars. Great pains were taken by the nursing staff to try to get the children to eat, as increase in amount of food taken and general improvement invariably occur simultaneously.

Specific treatment.—Eleven patients had no special treatment given save that some had massage; 2 were given thyroid extract, and 1 was given hydrochloric acid before food. These were used as controls in estimating the effect of other methods of treatment. Five were given liver, and 3 of them had a vitamin-B food (Bemax) in addition. Five patients were treated by ultra-violet light from a carbon arc lamp or vitamins A and D.

Three children were given intravenous or intraperitoneal sodium citrate with a view to bringing down the level of blood calcium. Two others were also given this treatment, but it was combined with keeping them in a room the windows of which were glazed with ruby glass, so that they were kept free from exposure to any rays from the violet end of the spectrum. Three patients received no treatment other than being kept in the red windowed room.

CONTROL PATIENTS.—The details of the cases used as controls were as follows:—

I. S., female, 14 months. One month's history. Massage; thyroid extract. Much improved in 6 weeks.

B. G., female, 8 months. Three months' history. Died a few days after admission.

L. Y., female, 10 months. Four months' history. Massage; thyroid extract. Discharged in 6 weeks apparently cured. Relapse 2 months later. (For treatment of relapse, see below.)

L. B., male, 17 months. One month's history. Owing to ward infection was discharged in a fortnight unchanged.

J. I., female, 26 months. Four months' history. Massage. Discharged improved in 6 weeks.

P. B., male, 12 months. One month's history. Was found to have low chlorides in gastric juice, and was given Acid. hydrochlor. dil., 10 min. t. d. s. Discharged improved in 1 month.

J. C., male, 10 months. Two months' history. Developed mumps 2 days after admission, for which he was discharged for 2 months. After readmission he remained in hospital for 2½ months and was discharged very much improved.

J. T. (a), female, 10 months. Five months' history. No treatment beyond general nursing. Discharged improved in 6 weeks.

A. T., female, 10 months. Two months' history. Massage. Discharged much improved in 6 weeks.

T. W., male, 12 months. Four months' history. Died 3 days after admission. Post-mortem not obtained.

A. C., male, 9 months. Four months' history. Died five days later. Post-mortem nothing abnormal save congestion of lungs and spleen and fatty infiltration of liver; horny layer of skin thickened.

The fatal cases all had a long history and were admitted moribund. The other patients usually recovered sufficiently to be discharged in about 6 weeks.

PATIENTS TREATED WITH VITAMIN B AND LIVER.—Five cases fall into this group:—

N. A., female, 15 months. Four months' history. Bemax 3 weeks, ? slight improvement. Malted liver given, after which patient became definitely worse. Treatment persisted in for a fortnight during which time she had persistent diarrhœa. Condition of child made it advisable to stop treatment. Bemax again given, followed by gradual improvement. Fit for discharge 3 months after admission.

J. S., male, 7 months. One month's history. Malted liver. Discharged by request in 3 weeks, slightly improved.

A. D., male, 6 months. One month's history. Diarrhœa on admission for which dietetic treatment (acid milk with casein, with malt added later) was given with satisfactory results in 18 days. The ½-oz. of raw liver ground up with port wine was given daily. Patient became ill with diarrhœa and treatment had to be abandoned. For further treatment see below.

K. L., female, 24 months. Three months' history. Bemax and raw liver. Was improving slowly in 2 months, but had to be discharged owing to measles in the ward.

K. M., 13 months. One month's history. Acid hydrochlor. dil., 5 min. t. d. s., tried for 3 weeks without improvement. Bemax and cod-liver-oil and malt then given. Slow improvement, but patient still ill after three months. Raw liver then given for a week. Patient lost appetite, vomited, developed diarrhœa, and became œdematous round the eyelids; lost all weight previously gained. Liver stopped, and Bemax and cod-liver-oil started again. Gradually improved, and was well enough for discharge 5½ months after admission.

From these 5 cases, 2 of which were treated by liver alone, and 3 by liver combined with Bemax, it appears that vitamin B has no marked effect, but that liver may be definitely harmful. It is not easy to explain the exactly opposite results obtained by Wyllie and Stern. Possibly their patients were benefited very considerably by being taken into hospital—one of them failing to show any improvement while treatment was being given at home, but immediately improving on being admitted. In Leicester the children's ward is modern, being particularly light and airy. It is conceivable that in the older and more venerable institutions of the metropolis the patients were not exposed to active daylight rays to the same extent.

Treatment by ultra-violet light and vitamins A and D.—The following are the details of the cases in this group:—

L. Y. After readmission for relapse slow improvement took place with U.V.L. Discharged very much improved in 3 months.

D. G., male, 12 months. Two months' history. U.V.L. Discharged improved in 6 weeks. Blood calcium, 13.10.31. = 11·6; 25.11.31. = 11·9.

B. P., male, 12 months. Three months' history. Was improving on admission. U.V.L. 6 treatments. Was discharged in a fortnight very much improved. Blood calcium, 14.6.32. = 11·7; 27.6.32. = 11·5.

J. T., female, 11 months. Five months' history. Radiostoleum for 3 months. No change.

K. M. In addition to treatment by liver and Bemax this patient had cod-liver-oil and malt, with no marked effect.

This treatment did not have much effect on the course of the disease. It is interesting to note that ultra-violet light did not alter the amount of calcium in the blood. Certainly the treatment did no harm. This may be due to the fact that both the carbon-arc and mercury-vapour lamps do not give off the short wave rays which may be the harmful ones. The improvement noted by Bruton Sweet[11], and suggested in 2 of the present series, may be due to a vaccine-like action, and gradually increasing doses producing immunity.

TREATMENT BY CITRATE INJECTIONS AND RED-WINDOWED ROOM.—(a) A group of cases received treatment by citrate injections only. The details were as follows:—

J. T. After this patient had been in hospital 3 months without improvement, half an ounce of a 3·5 per cent. solution of sodium citrate was injected intravenously. Within half an hour the child became much brighter in herself, but this immediate

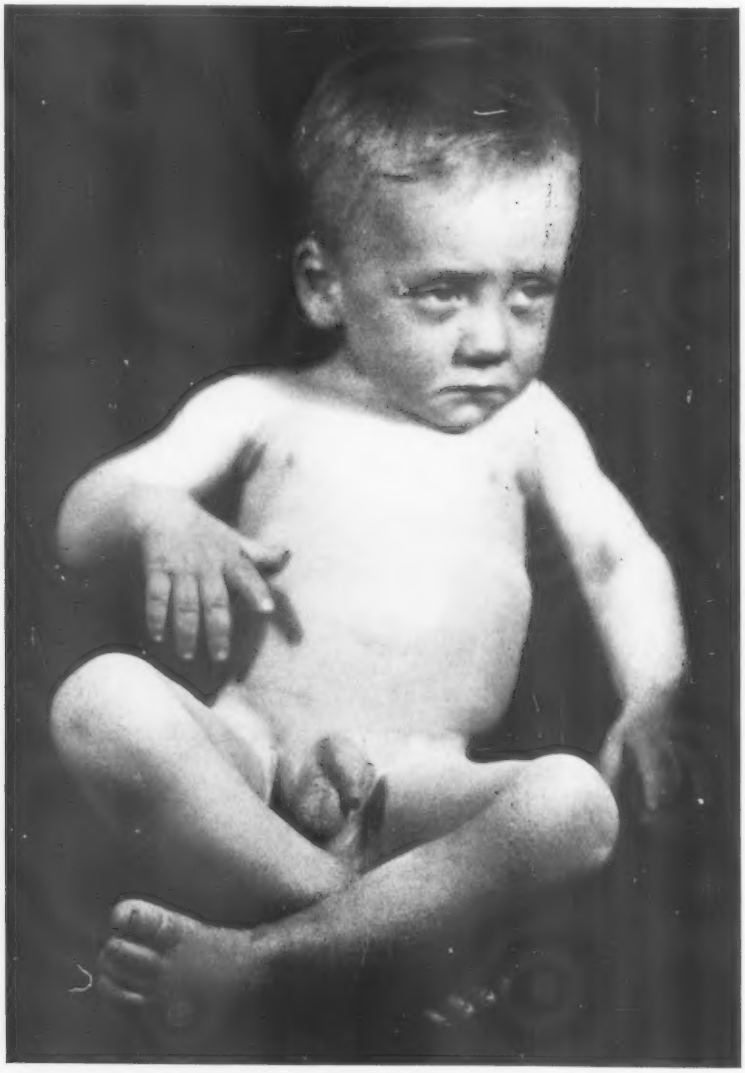


FIG. 2.—N. J., before treatment.

reaction only lasted a day or two, and the patient became atonic and unhappy again. However, steady, if slow, improvement set in, and although she had an attack of infective diarrhœa a month later, she was discharged 2 months after the citrate injection with convalescence well established.

A. D. When this patient had recovered from the effect of the liver (about a week after discontinuing it) 15 c.cm. of 3·5 per cent. sodium citrate solution and 10 c.cm. of normal saline were injected intraperitoneally. Immediately before the

injection, the blood calcium was 11·9 mgrm. per 100 c.cm. serum. The injection was repeated on the following day. Twenty-four hours later the child had definitely improved, the blood calcium being 10·9. Thereafter there was a steady gain in weight and improvement in general health, and the patient was discharged a month later doing well.

E. G., female, 6 months. One month's history. Blood calcium on admission was 12·3 mgrm. per 100 c.cm. serum. A week later 10 c.cm. of a 4 per cent. sodium citrate solution were injected intraperitoneally. On the following day the blood

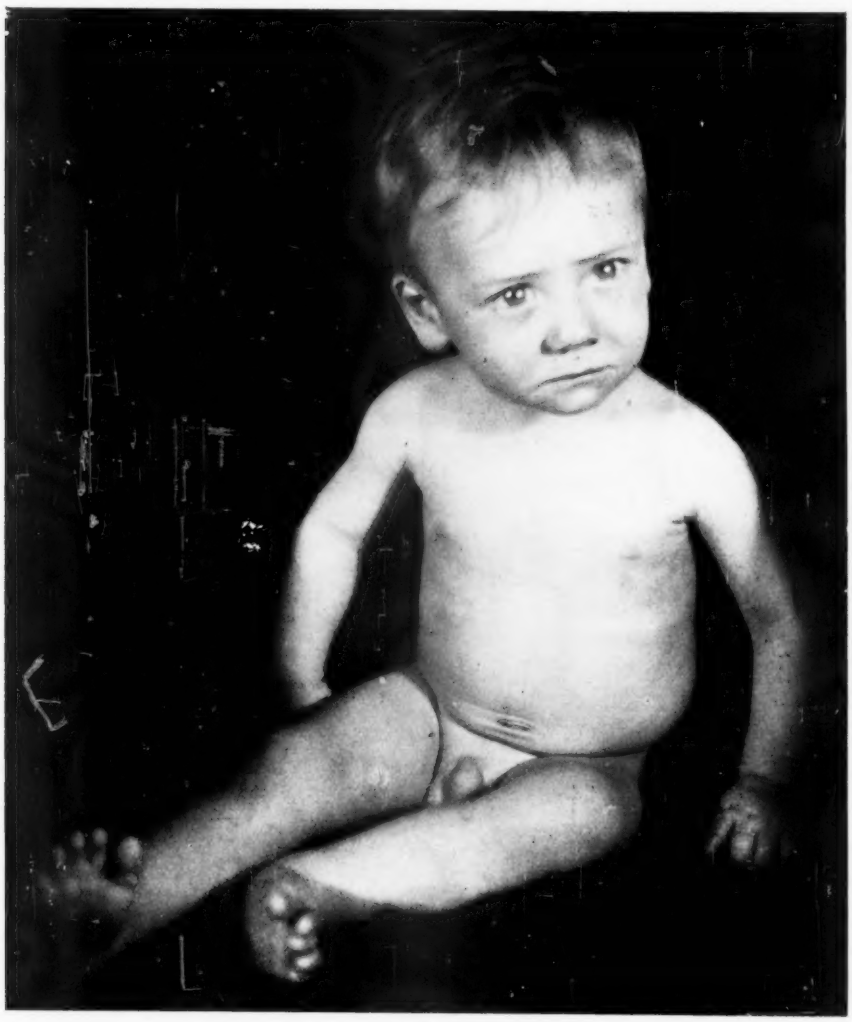


FIG. 3.—N. J., after treatment.

calcium was 10·4. The child improved rapidly in a week, sat up, and began to take food. The pink colour began to fade from the hands. Then the condition relapsed, and on the third day of the relapse a further injection of citrate was administered. The child again improved rapidly, and was discharged apparently well 6 weeks after admission.

R. D., male, 8 months. One month's history. 23.3.32. Blood calcium = 11·3 mgrm. 10 c.cm. 4 per cent. sodium citrate solution given intraperitoneally. Blood calcium after injection 10·5. By 25th was definitely better, and by 28th was able to stand,

On 31st the injection was repeated. Thereafter the child made a rapid recovery and was discharged apparently cured 7 weeks after admission.

From these 4 cases it appears that the injection of sodium citrate had an immediate beneficial effect on the patients, and that the blood calcium was lowered. The immediate effect wore off in a day or two, but steady improvement set in, although it cannot be claimed that the children's stay in hospital was much shortened.

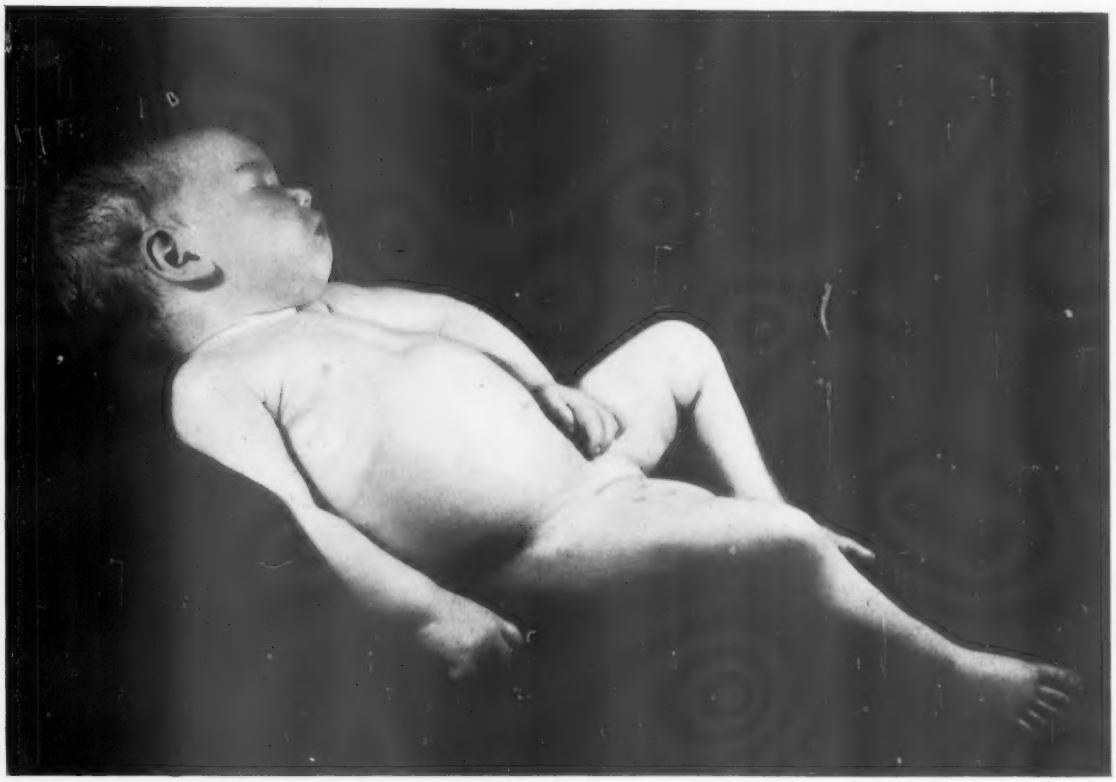


FIG. 4.—M. T., before treatment.

(b) Two children received treatment by citrate injections combined with the red-windowed room:—

N. J., male, 12 months. Two months' history. On April 28th his blood calcium was 11·7 mgrm. On May 6th 20 c.cm. 4 per cent. sodium citrate injected intraperitoneally. Two days later he was sitting up and holding up head, and was less pink about nose and hands. On May 9th he was not so well and was very limp again. Injection repeated, but no marked improvement followed. On May 23rd his blood calcium was 11·8. On 29th he was put into the red room. The child seemed unhappy for the first 24 hours, apparently missing the company of the other patients, but he took feeds well. In two days the muscle tone appeared normal, the child was sitting up and feeding well. Improvement maintained until June 6th when the blood calcium was 10·6. On this date owing to the ward being cleaned the patient had to be removed from the red room to a temporary ward. As there was an open-air balcony in this ward the experiment was cautiously made of putting the child in the sun (June 9). Within an hour the patient showed signs of great discomfort,

cyanosis, and collapse, and was at once removed into the ward where he gradually recovered. In 2 days the patient was able to go back to the red room, and 3 days later—a fortnight after his first going there—he appeared quite normal (Fig. 1 and 2).

This patient developed a small abscess in the leg, and on account of this remained in hospital for a further 3 weeks. The abscess cleared up normally after incision. He was seen at out-patients some weeks later and appeared perfectly well.

M. T., female, 6 months. Two month' history. For the first 3 weeks after admission there was no change. Blood calcium = 11·5 mgrm. On May 2nd, 1932,

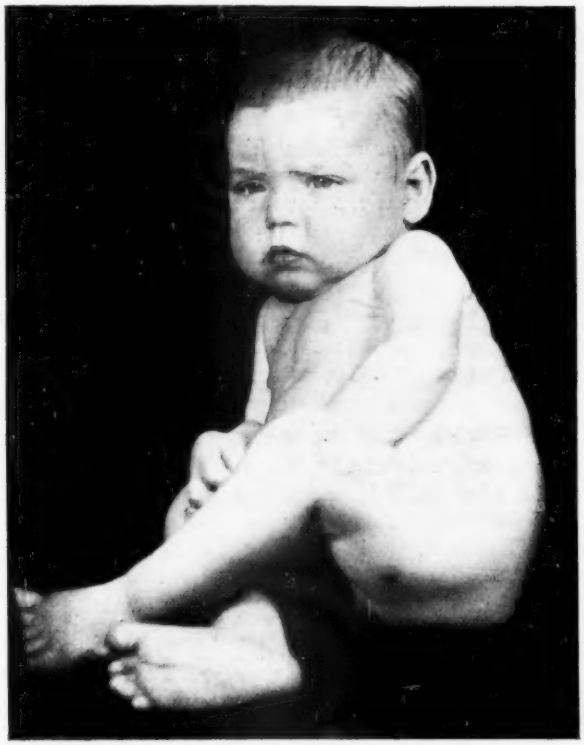


FIG. 5.—M. T., after treatment.

20 c.cm. 4 per cent. sodium citrate solution was injected intraperitoneally. No marked improvement. The injection was repeated on May 6th. Slow improvement started. Twelve days later the patient was smiling and taking feeds better. On May 21st the injection was repeated, and the next day she was not so well. On May 23rd her blood calcium was 12·5. On May 29th she was put into red room and was at first miserable and crying. By June 2nd there was definite improvement in muscle tone and mental condition. On the 5th she was removed from red room to temporary ward, owing to ward cleansing. Improvement was maintained, but blood calcium still 12·3. On June 11th she returned to the red room. Not so peevish this time. Rapid improvement set in, and on June 24th she was discharged feeding well, gaining 8 oz. a week, happy, with muscle tone much improved, 3½ weeks after being put into red room (Fig. 3 and 4). Seen at outpatients some weeks later, she was apparently normal.

Both these patients showed very marked improvement after being in the red-windowed room for 2 or 3 days. They did not respond to the citrate

treatment as well as the other patients had done. It is interesting that in one of them the blood calcium remained high, although the clinical symptoms had practically disappeared; and that in the other, exposure to sunlight had an alarming effect.

(c) Three patients received treatment by red-windowed room only. Unfortunately 2 out of these 3 patients contracted infectious diarrhœa and died. There was a mild ward epidemic, and although in the other children who suffered from the infection it produced only a trifling disturbance for a few days, both the patients with pink disease rapidly succumbed within 12 hours. However, as one has apparently recovered and was waiting to be discharged, and convalescence was well established in the other, their value as evidence of the efficacy of the treatment is unaffected.

P. C., male, 10 months. Four months' history. After a week in the red room sweating had disappeared, there was no photophobia, sleep was normal, and the appetite was improving. The patient then contracted the infection and died the same night.

Post-mortem report. Brain injected; considerable increase in cerebro-spinal fluid, but ventricles not distended. Fluid can be squeezed from both lungs, main bronchi injected. Heart, 1½ oz., slight hypertrophy of left ventricle; valves normal. Liver, 12 oz., appeared normal. Spleen, 1 oz., normal. Kidneys, 1 oz. each, normal. Suprarenals normal. Stomach normal. Some congestion of mucosa of ileum and colon with atrophy of Peyer's patches. Thymus, rather large, ½ oz. Thyroid normal. Spinal cord appears normal.

Sections. Spleen congested. Liver; fatty infiltration with dilated bloodvessels and some degeneration of cells. Thyroid appeared much more fibrous than normal, but there was a large amount of colloid present and the cells lining the acini appear normal. Brain normal. Spinal cord showed apparent increase in the neuroglia cells of the white matter, otherwise normal. Voluntary muscle normal.

K. M. (a), female, 7 months. Three weeks history. Blood calcium 11·2 mgrm. Apparently quite well after 1 week in red room, but blood calcium was 12·2. While waiting for discharge the patient developed infectious diarrhœa which proved fatal in 12 hours.

Post-mortem report. Brain congested and œdematous, no increase in fluid. Heart, 1¼ oz., slight hypertrophy of left ventricle; valves and myocardium normal. Lungs congested especially left lower lobe. Liver, 6 oz., pale and mottled. Spleen, 2½ oz., looks normal. Suprarenals, very little chromaffin substance seen. Pancreas and kidneys normal. Stomach walls thin, small spots of injection seen. Several terminal intussusceptions in small intestine. Some congestion of colonic mucosa. Thyroid normal. Spinal cord appeared normal.

Sections. Brain, no inflammatory change, neuroglia a little œdematous. Spinal cord showed similar apparent increase in neuroglia cells as previous case. Heart muscle normal. Liver showed very extensive fatty infiltration and great congestion. Spleen and kidney congested but normal. Thyroid of the fœtal type. Voluntary muscle normal.

G. W., female, 7 months. One month's history. Kept in ward for a fortnight, with no change in clinical condition. On October 22nd, 1932, blood calcium was 10·6. She was put into red room. By 25th she was happier, and was holding up head. By 30th she was sitting up; hands and feet were no longer pink; her limbs were firm, and she was taking feeds well. Her eyes were still running. She was taken back into ward. Eyes stopped running in four days. Discharged apparently cured 12 days from commencement of treatment.

From these 3 cases it appears that treatment by placing the patient in light from which the rays from the violet end of the spectrum have been excluded produces rapid recovery. The unfortunate death by infective illness of 2 of them perhaps suggest that the treatment may have a bad effect on resistance, but this is so notoriously bad in pink disease that it would be unwise to draw any further conclusions, except that especial care should be taken to prevent infection in patients who are being treated by this method.

Summary.

1. Pink disease occurs in children following or during an acute infection.

2. It occurs chiefly among well cared for children in good surroundings. Twenty of the 27 cases reported came from country or suburban homes. It was first described in Australia, and has been reported from New Zealand, America, and Switzerland.

3. Only 4 of the present series of cases were admitted during the winter months.

4. The blood calcium is usually raised.

5. Erythrocytosis as well as leucocytosis is very common in this disease. There is also often an increase in the amount of hæmoglobin. The sedimentation rate may be greatly increased.

6. Intravenous or intraperitoneal injection of sodium citrate usually causes a marked temporary improvement.

7. Keeping the children in light from which the rays from the violet end of the spectrum have been filtered by means of ruby glass causes a rapid and lasting improvement in the condition. In 1 case exposure to sunlight produced symptoms of collapse.

Conclusions.

1. Pink disease is due to an abnormal reaction to daylight in an infected child. It is cured by keeping the child from daylight.

2. Further work is needed to confirm the above results, and to elucidate the problems of the blood chemistry and cytology.

My thanks are due to my house physicians for carrying out the treatment and for keeping the records, and to the entire staff of the pathological department of the Leicester Royal Infirmary for the difficult collection and examination of specimens.

REFERENCES.

1. Swift, H., *Australian Med. Cong., Children's Sect.*, Brisbane, 1914, 347, quoted by A. J. Wood, *Med. J. Austral.*, Sydney, 1921, I, 145.
2. Thursfield, H., & Paterson, D. H., *Brit. J. Child. Dis.*, Lond., 1922, XIX, 27.
3. Paterson, D. H., & Greenfield, J. G., *Quart. J. Med.*, Oxford, 1923, LXV, 6.
4. Parsons, L. G., *Practitioner*, Lond., 1930, CXXV, 146.
5. Byfield, A. H., *Am. J. Dis. Child.*, Chicago, 1920, XX, 347.
6. Harris, L. J., *Lancet*, Lond., 1932, i, 1031.
7. Hess, A. F., & Lewis, J. M., *J. Amer. Med. Ass.*, Chicago, 1928, XCI, 783.
8. Boas, M. A., *Biochem. J.*, Cambridge, 1927, XXI, 712.
9. Findlay, G., & Stern, R. O., *Arch. Dis. Child.*, Lond., 1929, IV, 1.
10. Wyllie, W. G., & Stern, R. O., *Ibid.*, 1931, VI, 137.
11. Sweet, G. B., *Ibid.*, 1930, V, 405.

THE NON-PROTEIN NITROGEN OF THE BLOOD IN HEALTH AND IN HEPATIC DISEASE

BY

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It is universally accepted that urea is formed in the liver, and there is a considerable amount of evidence that some is retained there, either unchanged or in an altered form. It is possible that this power of retention prevents the blood becoming flooded with urea after a meal rich in protein, much as the glycogenic function of the liver acts as a barrier to hyperglycæmia. If this is the case, the normal liver should prevent an undue rise in non-protein nitrogen after the ingestion of urea, while the diseased liver should permit the non-protein nitrogen of the blood to rise to an abnormally high level, and to remain elevated for an abnormally long period.

It was shown by Cohen and Levin[1] that the non-protein nitrogen of the blood rose only after a meal containing nitrogen. The accompanying table (Table 1) shows the results which I have obtained after (a) giving glucose,

TABLE 1.

THE INFLUENCE OF THE INGESTION OF GLUCOSE SOLUTION AND WATER ON THE NON-PROTEIN NITROGEN CURVE.

No. of case	Age in years	Disease	Substance given	Percentage N.P.N. in blood: mgrm. per cent.				
				Fasting level	Hours after ingestion of glucose or water			
					½ hr.	1 hr.	1½ hr.	2 hr.
1	10	Valvular dis.	Glucose	44·0	37·9	30·8	30·0	23·1
1	10	,, ,,	150 c.cm. water	40·9	25·6	23·1	25·0	—
2	10	Pulm. fibrosis	Glucose	33·3	33·3	28·0	28·0	—
2	10	,, ,,	150 c.cm. water	46·7	48·0	30·0	37·6	40·0
3	11	Conv. chorea	Glucose	44·6	32·4	30·0	25·0	20·0
3	11	,, ,,	Nil given	30·6	31·8	21·0	—	30·2
4	10	Renal calculi.	Glucose	35·2	27·3	29·2	34·0	25·5
4	10	,, ,,	Nil given	29·2	28·4	27·7	20·0	18·8
5	7	Conv. chorea	Glucose	51·0	37·0	35·0	33·7	37·0
5	7	,, ,,	Nil given	39·0	39·3	36·7	47·1	35·0

* This work was done during the tenure of a Muirhead Scholarship.

(b) giving water only, and (c) a continued fast. From a glance at the figures it is evident that a fall in the fasting level of the non-protein nitrogen took place after the administration of glucose solution, the most marked being in Case 3 where the level fell by almost 25 mgrm. At first it was thought that the glucose was responsible for the fall. When, however, the experiment was repeated on two of the children, but instead of glucose solution the same volume of water alone was given, a similar fall resulted. It now seemed as though it were the water itself which was the cause of the diminution in the non-protein nitrogen. A third experiment was tried on three of the children, to whom neither glucose nor water was given and again a similar fall in the non-protein nitrogen occurred. From this experiment it seems clear that the non-protein nitrogen was not influenced by the taking of either carbohydrate or water, and that the fall observed was due to the continued nitrogen starvation.

The ordinary non-protein nitrogen curve after the ingestion of urea does not seem to have been extensively investigated. Archer and Robb[2] studied the blood-urea curve in four healthy subjects after the ingestion of 15 grm. urea, and they concluded that it usually reached its maximum within half an hour and returned to the fasting level within two hours after the urea had been given. It seems hardly justifiable to base a standard of normality on so small a number of cases, especially as in one instance the blood urea was still considerably above the fasting level at the end of the 2-hour period.

Methods of investigation.—The first specimen of blood was taken at 9 a.m. when the patient had been fasting for at least 12 hours. In one or two instances the blood was taken from a vein, but in the majority it was taken from a needle puncture of the thumb. Johnstone[4] found no appreciable difference in the urea-nitrogen content of venous and capillary blood. Folin and Svedberg's[3] micro-method was used for the estimation of the non-protein nitrogen. After the fasting specimen of blood had been withdrawn the child was given 15 grm. urea dissolved in 120 c.cm. of water. As the children were thirsty the drink was almost always taken readily. In none of the subjects did vomiting or any other untoward symptom follow the administration of the urea. Samples of blood were withdrawn 30, 60 and 120 minutes after the urea had been given. When specimens of urine could be obtained the urea was estimated with a view to gauging the renal efficiency.

In order to determine the normal levels of blood non-protein nitrogen at various intervals after taking urea, a series of 12 cases convalescent from various diseases and injuries was examined. In none of the cases was there reason to suspect that there was any disturbance in metabolism. None of them had been recently anæsthetized and none was receiving drug treatment. The ages ranged from 4 to 12 years. Summaries of the case reports are given in the appendix.

The normal non-protein nitrogen curve.—The fasting non-protein nitrogen was found to lie between 18 and 40 mgrm. per cent. (Table 2). In all the cases a definite rise was observed within half an hour of the ingestion of the urea. The smallest increase noted was 4·6 mgrm. per cent. and the largest 35 mgrm. per cent., while the maximum value reached was 62·5 mgrm. per cent. One hour after the urea had been given 9 of the curves were continuing to rise. The most marked increase from the previous specimen was 14 mgrm., while the smallest was 2·6 mgrm., and the highest

TABLE 2.

NORMAL NON-PROTEIN NITROGEN CURVES FOLLOWING THE INGESTION OF 15 GRM. UREA.

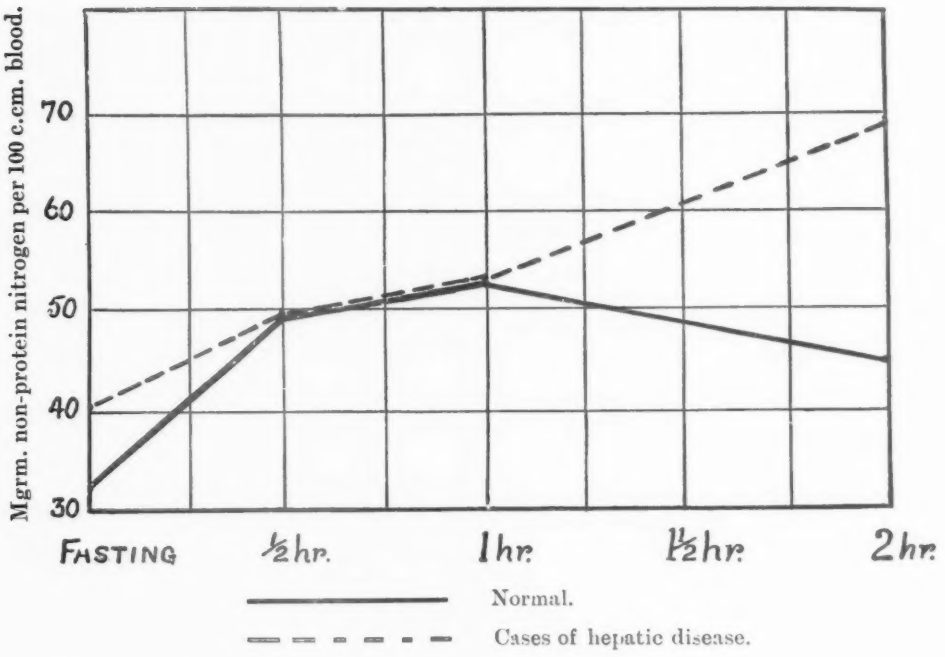
No of case	Age in years	Disease	Percentage of N.P.N. in blood: mgrm. per cent.			
			Fasting level	Hours after the ingestion of urea		
				½ hr.	1 hr.	2 hr.
1	4	Pulm. fibrosis	38·1	60·9	74·5	62·5
2	10	Neurosis	26·7	59·5	34·7	31·2
3	9	Spastic diplegia	18·0	32·6	46·8	39·3
4	8	Conv. ileo-colitis	33·0	38·0	45·0	35·0
5	8	Conv. purpura	31·3	42·3	30·5	30·0
6	11	Fracture	38·0	—	66·0	60·0
7	10	Conv. appendicitis	37·0	49·0	57·4	49·0
8	6	Fracture	33·1	50·0	52·6	50·0
9	13	Conv. chest wound	40·0	44·6	54·2	42·3
10	4	Conv. scalp wound	37·1	46·3	55·5	46·3
11	4	Mental deficiency	38·0	62·5	47·2	46·3
12	1	Conv. ileo-colitis	19·0	44·4	52·6	47·6

value attained was 74·5 mgrm. per cent. Three curves (Cases 2, 5 and 11) had by this time begun to return towards the fasting level. Two hours after the urea had been taken all the curves were on the downward trend, 3 had returned to within 2 or 3 mgrm. of the fasting level, 6 had fallen to within 20 mgrm. of the fasting level and 3 others were still more than 20 mgrm. above it. It is interesting to note that in both the oldest and the youngest of the group the apex of the curve had been reached within half an hour of the administration of the urea. This suggests that the size of the dose in relationship to the age of the child is of no moment. Taking these 12 cases into consideration it appears that the normal curve may be described as one

which reaches its maximum point within 2 hours of the ingestion of 15 grm. urea (Fig. 1).

FIG. 1.

BLOOD NON-PROTEIN NITROGEN AFTER 15 GRM. UREA.
COMPOSITE CURVE.



The non-protein nitrogen curve in liver disease.—Thirteen children in whom liver disease was known or suspected, were tested. The same procedure was followed as in the previous group. The ages of the children ranged from 1 to 10 years. The results are shown in Table 3, and summaries of the case reports are given in the Appendix. The fasting non-protein nitrogen lay between 26·7 and 52·6 mgrm. Thirty minutes after the urea had been taken all the curves, with the exception of one which remained stationary, were tending upwards. The rise at this stage was much less marked than that which occurred in the normal cases at the same stage, the average rise in this group being 8 mgrm. as compared with 16 mgrm. in the normal cases. One hour after the urea had been taken the values remained at practically the same levels as at 30 minutes. In one case only, a simple catarrhal jaundice, was there a rise of 15 mgrm. At 2 hours 6 had risen more than 20 mgrm. the greatest rise being in a case of catarrhal jaundice which increased from 39 to 79 mgrm. The curve in 5 cases had risen to a less degree, and in one case there was no change from the level found at one hour. Three hours after the urea had been given 3 curves were continuing to rise. By 4 hours all had begun to descend, and those which were estimated at 5 hours showed a further fall towards the fasting level.

TABLE 3.

NON-PROTEIN NITROGEN CURVES IN HEPATIC DISEASE FOLLOWING THE INGESTION OF 15 GRM. UREA.

No. of case	Age in years	Disease	Percentage of N.P.N. in blood: mgrm. per cent.						Urea concentration test grm. per cent.		
			Fasting level	Hours after ingestion of urea							
				½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	Fasting	1 hr.	2 hr.
1	3½	Catarrhal jaundice	30·0	36·2	39·0	79·0	—	—	—	—	—	—
2	8	,, ,,	47·6	47·6	51·0	57·4	66·6	—	—	1·82	2·00	2·18
2	8	,, ,,	42·7	52·6	67·5	67·5	70·0	62·5	52·6	—	—	—
3	5	,, ,,	49·0	—	67·5	—	72 5	—	—	2·18	4·02	3·99
4	8	,, ,,	35·0	50·7	58·9	68·5	55·0	—	—	2·74	3·93	3·33
5	5	,, ,,	40·0	51·9	50·1	69·4	74·0	—	—	—	—	—
6	1	,, ,,	52·6	54·3	59·5	69·4	—	—	—	—	—	—
7	8	Banti's dis.	45·4	50·0	50·4	76·0	—	—	—	—	—	—
8	10	,, ,,	35·2	44·6	—	52·6	50·0	52·0	40·0	3·69	3·79	3·56
9	9	,, ,,	48·5	49·5	52·6	70·6	—	—	—	—	—	—
10	1	Biliary cirrhosis	34·0	44·6	44·0	52·6	44·0	34·7	29·4	2·82	2·37	2·68
11	4	Cholecystitis	26·7	30·0	52·5	71·4	—	—	—	—	—	—
12	9	Hepatic enlargement	47·1	56·8	56·0	74·6	74·0	55·5	—	—	—	—
13	3	,, ,,	34·2	—	60·0	91·0	—	—	—	1·86	2·73	3·14

The curves obtained following the administration of urea in hepatic disease differ in three main points from the curves found in normal individuals. These are (1) the higher average fasting non-protein nitrogen, (2) the slow rise, and (3) the height and prolongation of the curve. On account of the high fasting non-protein nitrogen it might be suggested that some disorder of the kidneys was responsible for the abnormal curves. In order to eliminate this possibility urea-concentration tests were carried out on 6 of the patients. The results which are shown in Table 3 were satisfactory in all the cases. The lowest fasting value was 1·82 grm. per cent. and the lowest level reached after the ingestion of the urea was 2 grm. per cent. while the majority were considerably higher. In Case 3 where the fasting non-protein nitrogen was 49 mgrm. per 100 c.cm., the urinary urea rose from 2·18 grm. to 4·02 grm. after the urea had been given. From this example it would appear that inefficiency in excreting urea is not a cause of the high fasting non-protein nitrogen or of the abnormal curve.

The most plausible explanation of the increased fasting non-protein nitrogen appears to be that the liver is unable to retain the end-products of endogenous protein metabolism which thus accumulate in the blood. The delayed rise in the curve is possibly due to some defect in absorption from the bowel. The height and prolongation of the curves may be due to the diminished power of the diseased liver to retain or store the non-protein nitrogen.

Summary.

1. The non-protein nitrogen curve following 15 grm. urea in normal fasting children is described.

2. The non-protein nitrogen curve following 15 grm. urea in fasting children suffering from various forms of hepatic disease was found to be more prolonged than in normal subjects.

3. It is suggested that the non-protein nitrogen curve may prove a useful test of hepatic efficiency.

It is a pleasure to acknowledge my indebtedness to Professor G. B. Fleming and Dr. Noah Morris for their valuable advice and criticism. My thanks are also due to Dr. Stanley Graham and Mr. Matthew White for granting me facilities for examining cases in their wards.

REFERENCES.

1. Cohen, P., & Levin, S. J., *Arch. Int. Med.*, Chicago, 1927, XXXIX, 787.
2. Archer, H. E., & Robb, G. D., *Quart. J. Med.*, Oxford, 1924, XVIII, 274.
3. Folin, O., & Svedberg, A., *J. Biol. Chem.*, Baltimore, 1930, LXXXVIII, 85.
4. Johnstone, C., *J. Clin. Invest.*, N.Y., 1931, IX, 209.

Appendix.

Summaries of case reports.

Case 1.—Boy, 3½ years. Previous history, not important. Vomiting for 9 days, accompanied by dark urine and white stools. Jaundice of 4 days duration. Liver palpable 1½ in. below costal margin. Urine contained bile pigment.

Case 2.—Girl, 8 years. Previous history, not essential. Nausea and anorexia for 7 weeks. Intermittent jaundice for 4 weeks accompanied by light coloured stools, dark urine and occasional vomiting. Liver 4 in. below costal margin. Wassermann reaction negative. Microscopic blood examination, secondary anæmia. Fragility of red cells normal. Van den Bergh: 32 units, biphasic.

Case 3.—Girl, 5 years. Previous history, not essential. Loss of appetite and irritable 6 days ago. Next day vomiting began and was accompanied by jaundice, pale stools, dark urine and itchiness of the skin. Liver 2 in. below costal margin. Wassermann reaction negative. Microscopic blood examination, secondary anæmia. Van den Bergh: biphasic reaction, 14 units.

Case 4.—Girl, 8 years. Previous history, unimportant. Nausea and anorexia for 4 days. Vomiting, constipation and abdominal pain for 3 days. Jaundice for 2 days.

Case 5.—Boy, 5 years. Previous history, acute rheumatism August, 1931. Heart not affected. Jaundice of 4 days duration accompanied by vomiting. Liver border 2 in. below costal margin.

Case 6.—Girl, 1 year and 4 months. Healthy baby, but always pale. Jaundice for 1 week. Liver palpable but not enlarged. Spleen 2 in. below costal margin. Microscopic blood examination, secondary anæmia. Trace of urobilin in urine. Van den Bergh: direct, negative; indirect, positive.

Case 7.—Girl, 8 years. Previous history, not important. Intermittent jaundice for 2 years. Constant for 6 months. During attacks stools are white and urine dark. Two months ago abdomen began to swell. Liver and spleen greatly enlarged. Urine; urobilin present, bilirubin absent. Fragility of red cells not increased. Van den Bergh: biphasic reaction, 11 units of bilirubin.

Case 8.—Girl, 10 years. Healthy until 7 years of age when in hospital with diphtheria, enlarged spleen found. Child otherwise well. Skin dark, pigmentation of flexures. No jaundice. Liver and spleen both enlarged. No glandular enlargement. Blood picture, secondary anæmia. Fragility of red cells not increased. Urine, no bile pigment. Van den Bergh: direct, negative; indirect, 2 units. Splenic puncture, Banti's disease.

Case 9.—Girl, 9 years. Adopted child, previous history unknown. On day of admission headache and vomited about 5 oz. bright red blood followed 2 hours later by vomiting of dark brown material. Physical examination negative. Benzidine test on stool, positive. Lævulose curve, positive.

Case 10.—Boy, 1 year. Diagnosis, biliary cirrhosis. Since birth has had 5 attacks of jaundice, accompanied by light stools and dark urine, which cleared within 1 week. Irritable and loss of appetite for 1 month. Swelling of abdomen noticed 2 weeks ago. Liver and spleen both greatly enlarged. Van den Bergh reaction: direct, negative; biphasic, positive; indirect, 3·5 units of bilirubin. Fragility of red cells, unaltered. Wassermann reaction, negative. Blood picture, secondary anæmia.

Case 11.—Boy, 4 years. Healthy until last 5 weeks when he became listless and lost his appetite. Vomiting and right-sided abdominal pain for 4 days. Motions loose, urine dark. No jaundice. Abdomen tender and resistant. Fever present. At operation, gall bladder greatly distended and liver reached to umbilicus. No stones were found. Urine, no abnormal constituent. Lævulose tolerance test, positive.

Case 12.—Boy, 9 years. Swelling of abdomen dating from infancy. No symptoms. Liver 3 in. below costal margin. Lævulose curve, positive. Fifty per cent. rise in blood-sugar value following the ingestion of lævulose.

Case 13.—Girl, 4 years. Previous history, pyuria. General health good. Active child. Liver 2 in. below costal margin. Urine clear. Blood urea, 19·1 mgrm. per cent.

ATELECTATIC BRONCHIECTASIS IN CHILDHOOD

BY

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The occasional occurrence in radiograms of the chest of triangular shadows, situated behind the heart-shadow on the left or across the cardio-phrenic angle on the right, has attracted the attention of radiologists for many years. It is, however, only since the introduction of lipiodol for diagnostic purposes that the frequent association of these shadows with bronchiectasis has been recognized. Many of the earlier writers on the subject regarded the triangular shadow as being diagnostic of a mediastinal effusion, as described by Dieulafoy[1], but almost consistently negative results on needling and the absence of fluid when open operation was adopted (Sergent and Bordet[2]) led to the realization that effusion could only rarely be held responsible. Rist, Jacob, Trocmé, and Soulas[3, 4] recognized the presence of bronchiectasis in a number of classical cases which they described, and considered that the shadow was due to the formation of a secondary ' adhesive mediastinal pleurisy ' over the bronchiectatic area, associated with pneumonic infiltration within it. A similar interpretation has been accepted by the majority of French clinicians who have described cases. In England and America the triangular shadow is generally regarded as being due to collapse of the lower lobe, or of an accessory lobe, of the lung, though this view does not of course exclude the possibility of pneumonic consolidation or fibrosis within it, nor of thickening of the pleura with which it is covered.

The term ' atelectatic bronchiectasis ' has therefore been applied to the cases in which there is dilatation of the bronchi within the collapsed area; the evidence for this interpretation will be discussed subsequently. Cases have been reported in this country by Sparks[5], Morlock and Pinchin[6], Ellis[7], and Rodgers[8], and the condition has been considered from the clinical and radiological points of view by Moll[9] and Kerley[10] respectively. There is little doubt, however, that the condition is more frequent than the extent of the literature might imply.

Present investigations.

It is with the object of illustrating certain clinical features of the condition as it occurs in childhood that the following eight cases are reported. Five show the classical picture, while three others are included for the light they throw on the ætiology and pathogenesis. All have been under observation in the Children's Department of the London Hospital during the past two years.

LIPIODOL INVESTIGATION.—All the cases except one were investigated by the injection of lipiodol. This was carried out by the crico-thyroid route through a small needle, using 10 c.cm. lipiodol. This amount is rather more than is generally recommended for children, but no ill effects are likely to follow if the injection is carried out sufficiently slowly. The children were given 1½ grn. of nembutal by mouth and ¹/₁₂ grn. of morphia subcutaneously three-quarters of an hour before the injection. In some cases the nembutal produced a satisfactory state of drowsiness in which it was possible to carry out the injection under local anæsthesia of the neck and cocainization of the trachea. In most instances, however, it was found more satisfactory to give a general anæsthetic, for which nembutal served as an excellent, though somewhat uncertain, preparation, in order to abolish the cough reflex, the child being kept lightly anæsthetized until it was seen from the first film whether adequate filling of the collapsed area had occurred. The injection was carried out with the child lying supine with the shoulders raised on a single pillow and the neck extended. As soon as the injection was completed, the shoulders were raised on a second pillow and the child turned on to the affected side. In four cases the filling of the affected area was rapid and complete, while in three the lipiodol entered the collapsed lobe less readily than the surrounding lung.

True atelectatic bronchiectasis : Cases 1-5.

Cases 1 and 2.—Bronchiectasis limited to a collapsed area behind the heart-shadow.

Case 1.—(Fig. 1) No. 40867.—B. H., a girl, aged 8½ years. Infancy and development were normal until 1927 when at the age of 3 years she had broncho-pneumonia and is said to have been ill for nearly 5 months. She attended the out-patient department in 1929 (aged 4¾) on account of persistent cough. Her weight was then 32½ lb. Crepitations were heard over both lower lobes posteriorly. The Pirquet test was negative. Since this time the chest signs have persisted, and there has been intermittent cough, more frequent in the winter. Sputum has only occasionally been present with exacerbations of the cough, and has never been fœtid. In January, 1930, when she was 5 years old, slight clubbing of the fingers was first noted. The general health has been moderately good except for occasional attacks of 'bronchitis' during the winter, although she has been consistently somewhat under-weight for her age. In June, 1932, she was admitted to hospital for investigation.

On examination: A moderately well-developed child with good colour, weighing 44 lb.; no cough whilst in hospital. Postural drainage failed to produce sputum. The fingers showed a slight degree of clubbing. The chest was not deformed and moved evenly. The apex beat was in the 5th intercostal space in the mid-clavicular line. There was no impairment of the percussion note, but slight diminution of air-entry at the left base. Coarse râles were heard at both bases posteriorly. No other physical signs of disease were present except caries of 3 molars.

Radiological examination: An area of increased density behind the heart-shadow, extending from the hilum of the left lung to the diaphragm, is seen in repeated films taken since the patient's first attendance in 1929.

Lipiodol injection (June, 1932) showed bunching together and cylindrical dilatation of the bronchi within the collapsed area, and spreading-out of the bronchi and emphysema of the upper lobe (Fig. 1).

Since this time, the physical signs have not altered appreciably; she now weighs 47½ lb. (normal 52½ lb.), and with the exception of infrequent cough has at present no symptoms.

Case 2.—(Fig. 2 and 3) No. 40439.—R. B., a girl, aged 9½ years. The child was well until the age of 3¼ years (1926), when she had pneumonia, followed by persistent cough, which was most troublesome at night. She was brought to hospital in 1928, at the age of 4½, on account of this symptom. At this time the percussion note was normally resonant over both lungs, and air-entry equal, but dry rhonchi were heard at both bases posteriorly. The heart was not displaced; there was no clubbing. Cough produced a moderate amount of yellow sputum. The tonsils, which were

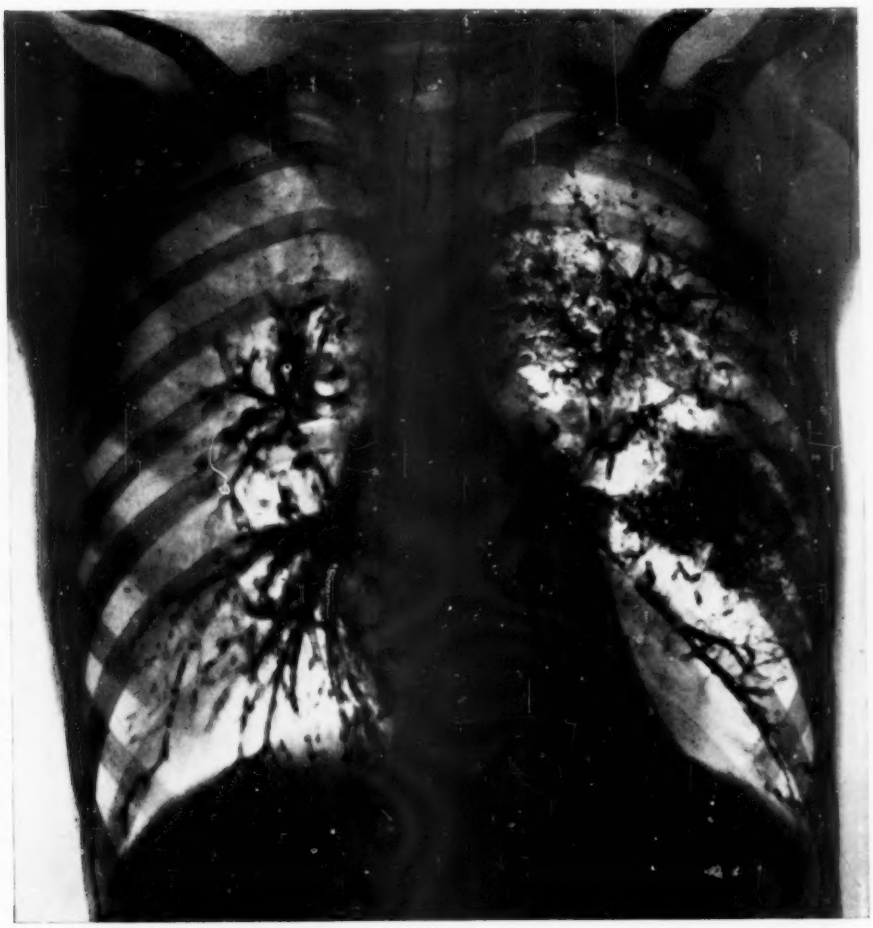

FIG. 1.—Case 1. B. H. Dilatation and bunching together of bronchi within collapsed left lower lobe, and spreading-out of bronchi of left upper lobe.

large and unhealthy, were removed when she was 5. At this time she weighed 33 lb. The cough becoming much less troublesome, she failed to re-attend the out-patient department until September, 1931, when, at the age of 8, she weighed 37 lb. Severe but unproductive cough had recurred for the past 6 weeks. A radiogram taken at this time shows evidence of a collapsed area behind the heart. The Mantoux test was negative (1 in 1,000 dilution). The child was sent to a convalescent home for 2 months. On her return, examination of the chest showed many crepitations at both bases posteriorly, with an area of tubular breathing below the angle of the

left scapula. Early clubbing of fingers was noted. She was admitted to hospital for lipiodol examination in March, 1932.

On examination: A thin but otherwise healthy-looking child, with marked fœtor of the breath. Weight 37½ lb. (normal 53 lb.). A slight degree of clubbing of the fingers was present. There was considerable muco-purulent post-nasal discharge and caries of several teeth. The chest moved evenly; there was no displacement of the heart. The percussion note was impaired at the left base, and there was diminished air-entry in this area. Coarse crepitations were heard at the right base, and an area of tubular breathing at the angle of the left scapular.

Lipiodol injection showed typical bronchiectasis and bunching together of the bronchi within the collapsed area behind the heart shadow (Fig. 3).

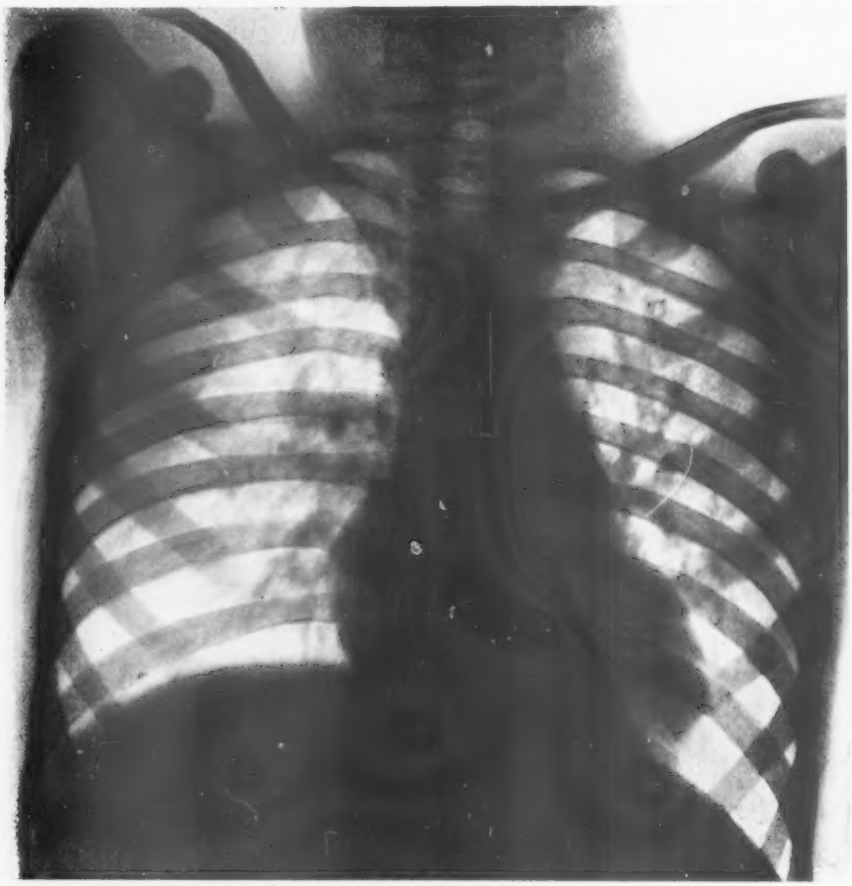

FIG. 2.—Case 2. R. B. Collapsed left lower lobe behind heart shadow.

Since her discharge from hospital, the child has been admitted to an open-air school and her general health has been good, though the gain in weight has been poor. Cough has not been severe or productive. The physical signs have remained unchanged, except that the breath sounds are now definitely amphoric rather than tubular in the small area at the angle of the left scapula. She now weighs 43 lb. at the age of 9½ (normal 57½ lb.).

Cases 3 and 4.—Left-sided atelectatic bronchiectasis with dilatation of adjacent bronchi.

Case 3.—(Fig. 4) No. 41876.—M. M., a girl, aged 9 years. The mother died 3 years ago from rheumatic carditis; the father attends hospital with chronic bronchitis; one sister is alive and well. The patient was well except for repeated attacks of bronchitis until September, 1928 (age 5), when she suffered from broncho-pneumonia following measles, and was in Bethnal Green Hospital for 6 weeks. Since this time she has had persistent cough, and was brought to the London Hospital in February, 1929, on account of this symptom. At this time the chest showed flattening at the left base, and impaired percussion note with absent breath sounds over the left lower lobe. The Pirquet test was negative. Radiological examination (Feb. 8, 1929) showed a triangular shadow behind the heart shadow and increased lung markings at the right base. She was admitted to hospital in March, 1929, when she had frequent cough and persistent signs at the left base. The apex beat was in

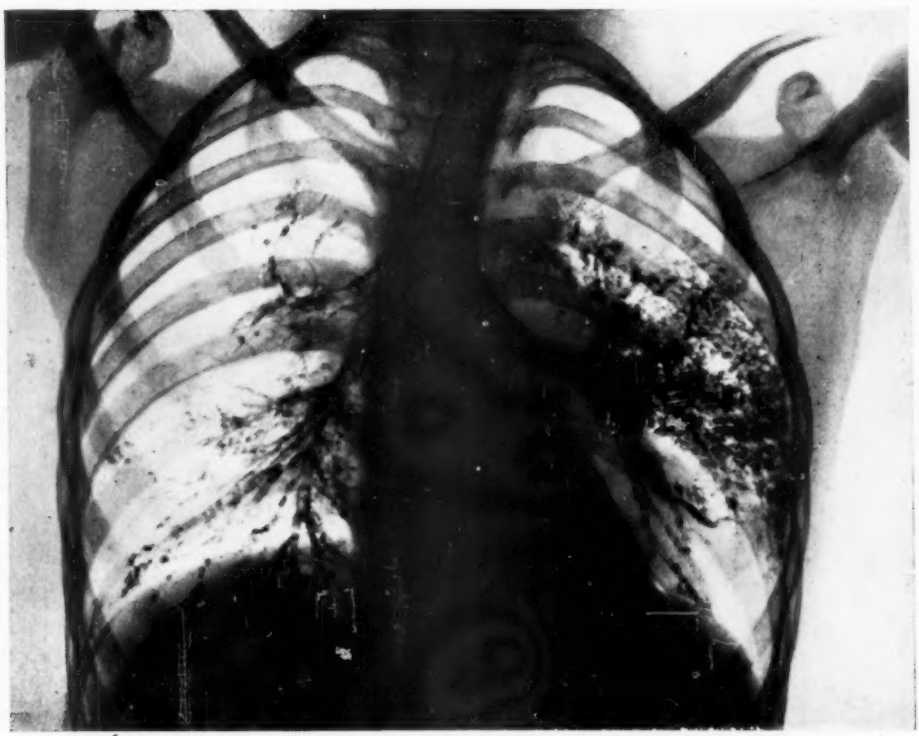

FIG. 3.—Case 2. R. B. Dilatation of bronchi within collapsed left lower lobe.

the 4th space ½ in. external to the mid-clavicular line. There was no clubbing. She was discharged to long convalescence, but in August, 1929, the radiogram of the chest was unchanged. She was admitted to a residential school until November, 1932, and during this period had persistent cough with a little non-purulent sputum. She suffered from broncho-pneumonia for the second time in December, 1930, but otherwise her general health has been moderately good. She was admitted to hospital for lipiodol examination in December, 1932.

On examination: A moderately well-developed child weighing 52 lb. (normal 55 lb.). Her colour is good; there is no clubbing. There is marked pigeon-breast deformity of the chest, with flattening of the lower ribs anteriorly on both sides, and slight flattening and diminished movement of the left side of the chest posteriorly. The apex-beat is visible in the 4th and 5th spaces ¼-in. outside the mid-clavicular line. The percussion note is slightly impaired in the left mid-axillary

line to the level of the 4th rib above, and there are scattered rhonchi heard over the left lower lobe posteriorly. Air entry is equal on the two sides. There was frequent unproductive cough while the child was in hospital.

Radiological examination: Generalized increase of lung markings with fibrosis of right zone 3 and collapse of the left lower lobe.

Lipiodol injection showed bunching together and dilatation of the bronchi within the collapsed area and an appearance suggestive of varicosity of the two adjacent bronchi. The remainder of the bronchial tree appeared normal.

Case 4.—(Fig. 5) No. 30748.—C. F., a boy, aged 13 years 3 months: an only child; both parents well. Infancy was normal. Pneumonia followed measles when he was

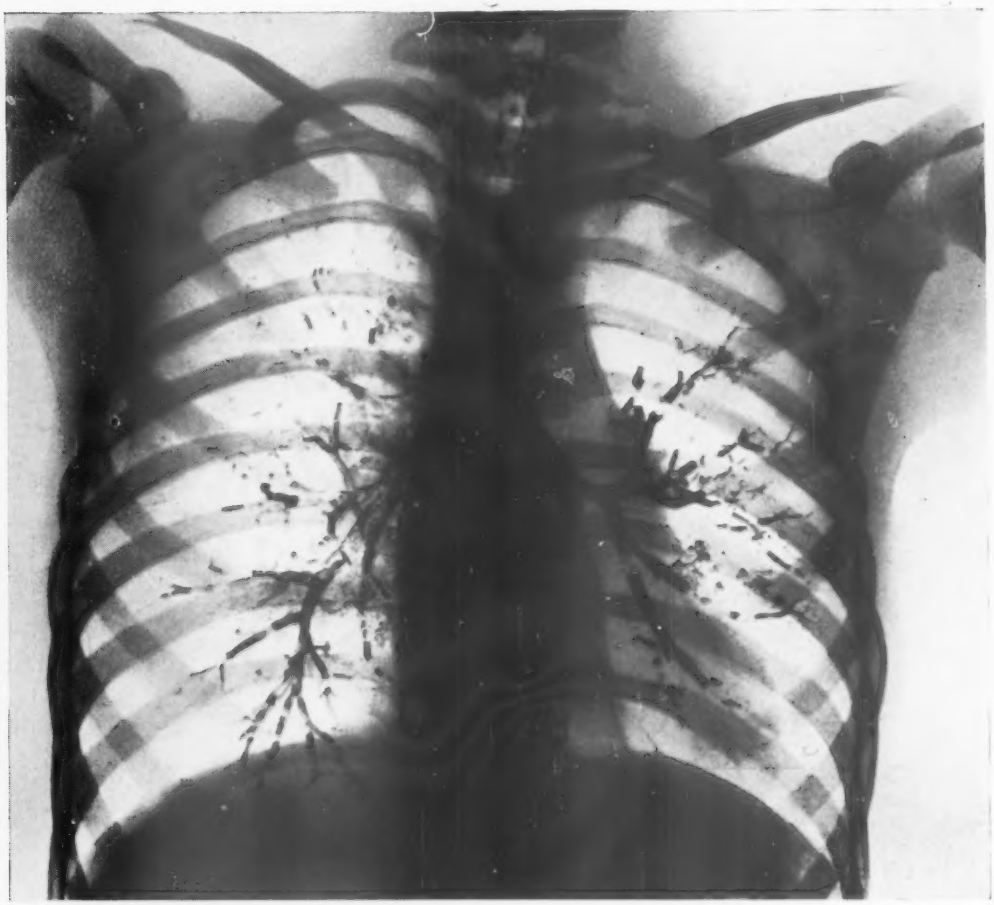

FIG. 4.—Case 3. M. M. Dilatation and bunching together of bronchi within collapsed left lower lobe and ' varicose ' appearance of two adjacent bronchi.

4½ years old, since when he has had cough which occurs throughout the day and is usually unproductive. He has had a variable amount of sputum, which has never been noticeably offensive, and recently has been almost entirely absent. His general health has been good. He was first seen at the London Hospital in April, 1927, at the age of 7½, when slight clubbing of the fingers was noted and examination of the chest showed impaired percussion note with crepitations and occasional rhonchi at the left base; air-entry appeared normal. The apex-beat was 1 in. to the left of the mid-calvicular line in the 5th intercostal space; the heart sounds were normal.

Radiological examination showed an increase of lung-markings at the right base, the left base being obscured by the heart shadow. Repeated X-rays since this time have shown the presence of a sharply-demarcated area of increased density behind the heart shadow. As in several of the long-standing cases, the opacity is not strictly-speaking triangular in shape, the hypotenuse of the triangle running almost vertically downward from the region of the hilum to the diaphragm.

Lipiodol injection (April 4, 1932) was unsuccessful owing to vomiting during the procedure, but a second injection carried out (June 6) showed bronchiectasis within the collapsed area, and marked dilatation of the two adjacent bronchi. The remainder of the bronchial tree appeared normal.

Orthodiagraphic examination (Dr. William Evans) showed the heart displaced to the left, but revealed no obvious abnormality of the heart chambers.

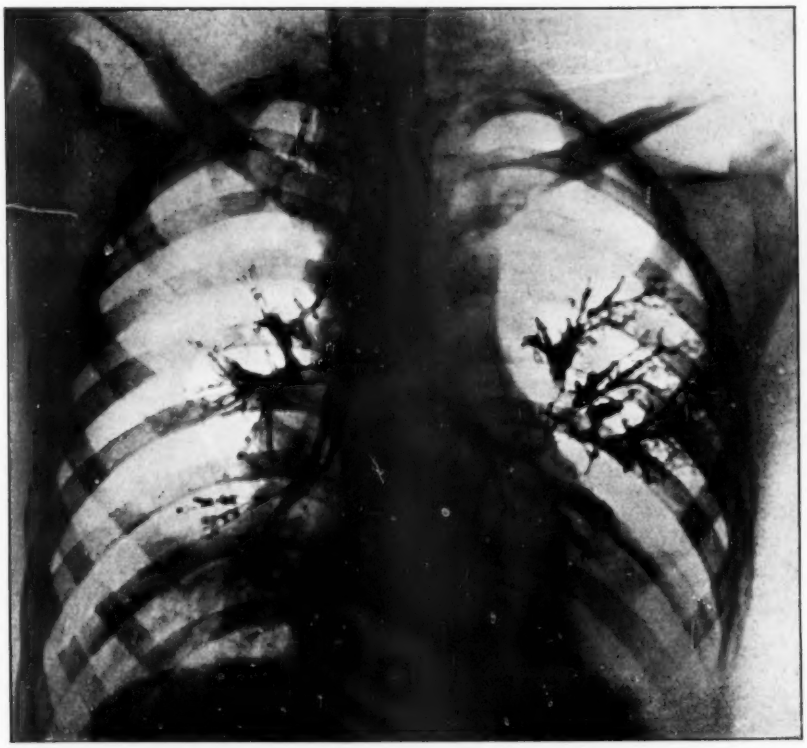

FIG. 5.—Case 4. C. F. Displacement of heart, bronchiectasis within collapsed area behind heart shadow, and dilatation of two adjacent bronchi.

Considerable constitutional disturbance followed the first injection of lipiodol, with dullness of the percussion note and diminished air-entry at the right apex, lasting 3 or 4 days. Sputum examination was negative for tubercle bacilli. In May, 1932, 2 weeks after the injection, the boy developed acute hæmorrhagic nephritis, but made an uneventful recovery. Since this time he has been in excellent general health, and has been all but free from both cough and sputum for 3 months.

On examination (Dec., 1932): A well-developed and nourished boy, weighing 91½ lb. (normal 85 lb.). Height 4 ft. 10½ in. The apex-beat is in the 6th intercostal space on the left, in the anterior axillary line. There is a soft localized systolic murmur in the mitral area. The thyroid is slightly enlarged. The chest moves evenly; there is no appreciable scoliosis, but slight flattening of the left lower ribs.

The percussion note is impaired at the left base posteriorly, and rhonchi are heard in this area on deep inspiration. There is a small area of bronchial breathing below the angle of the left scapula. The fingers show a moderate degree of clubbing.

The report and illustration of this case are included by courtesy of the Honorary Editors of the Proceedings of the Royal Society of Medicine.

Case 5.—Bronchiectasis at both bases with bilateral atelectasis.

Case 5.—(Fig. 6 and 7) No. 30174.—L. A., a boy, aged 9½ years. Parents and 4 siblings are alive and well; 1 child was still-born. Infancy was uneventful until the age of 8 months, when the patient had whooping-cough followed by broncho-pneumonia. Since this time he has had persistent cough of variable severity. There

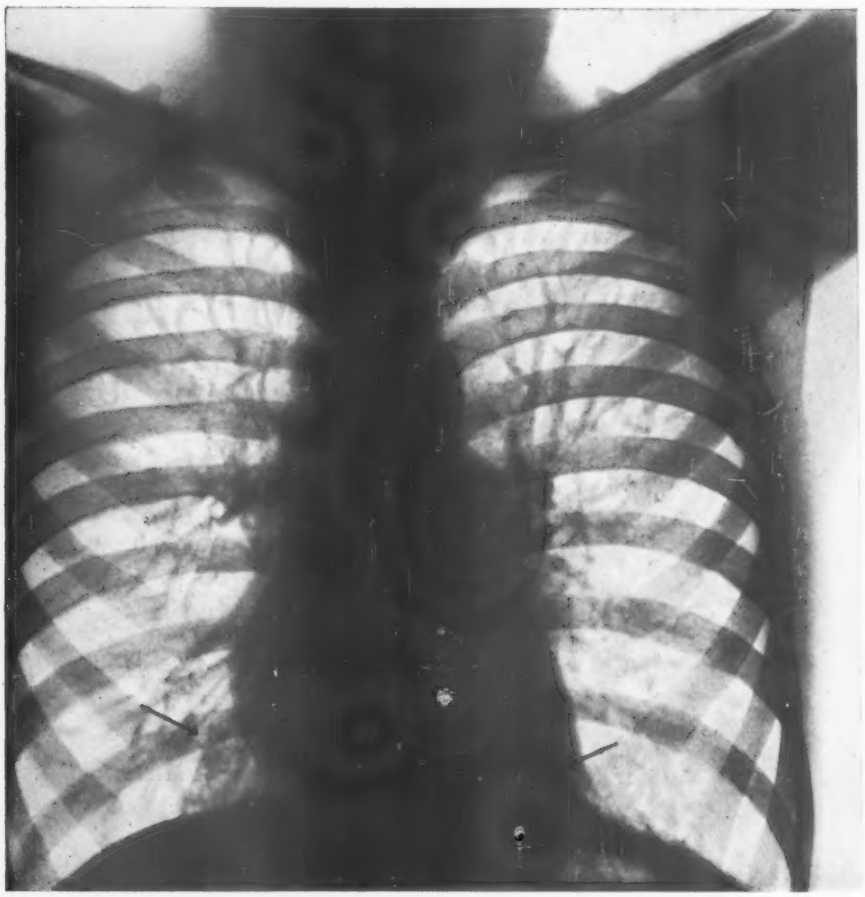

FIG. 6.—Case 5. L. A. Bilateral atelectasis. On the left the collapsed area is almost entirely obscured by the heart shadow.

has been little or no sputum except during occasional exacerbations of the cough in winter. He has played games normally, and the general health has been good. He was first seen at the London Hospital in 1929 at the age of 5¾ years on account of the cough. He was then of normal weight for age, and appeared well. There was clubbing of the fingers, and crepitations and rhonchi were heard at both bases posteriorly. No other abnormal physical signs were detected.

Radiological examination of the chest showed heavy hilar shadows with no definite evidence of fibrosis, but a well-defined triangular shadow across the right cardiophrenic angle. A subsequent examination in the left semi-oblique position showed in addition an area of collapse behind the heart shadow on the left.

He was sent away for prolonged convalescence in 1930. Since this time the boy gained weight steadily, and apart from cough and frequent night-sweats has suffered but little disability. The physical signs and X-ray appearances have remained almost unchanged since the first observation, though râles are now more marked throughout the right lower lobe than on the left. He now weighs 64 lb. (normal 64 lb.). Sputum examination was negative for tubercle bacilli.

Lipiodol examination in October, 1932, showed cylindrical bronchiectasis at both bases. On the right side this appears to be principally limited to the collapsed area, with some dilatation of the adjacent bronchi, but on the left the bronchiectasis is more extensive. The area of collapse in this case does not appear to involve the whole of the left lower lobe.

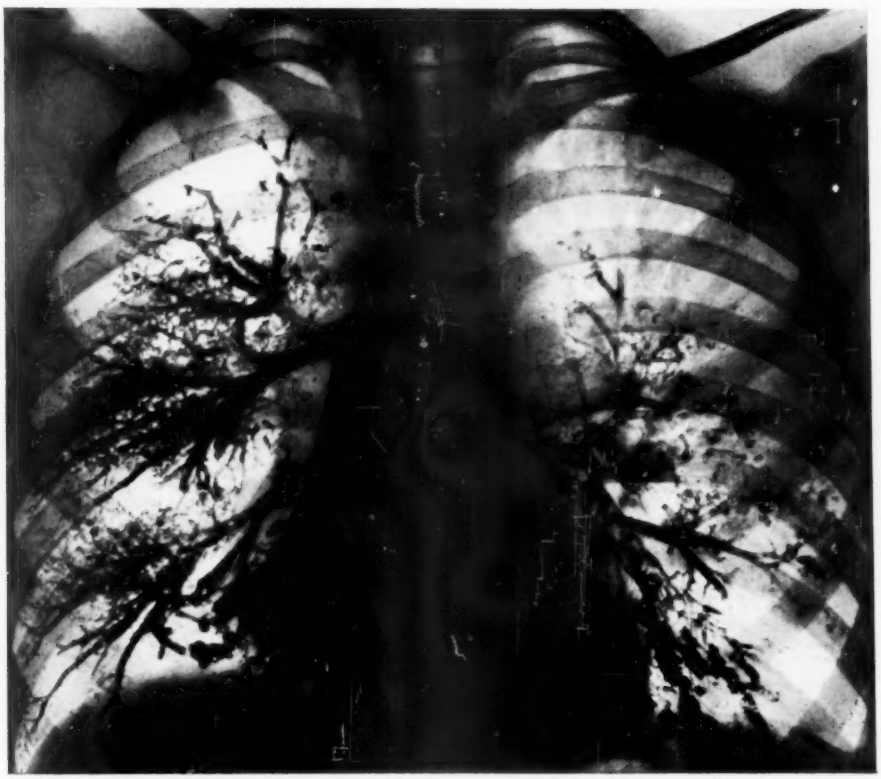

FIG. 7.—Case 5. L. A. Bilateral bronchiectasis. On the right this is mainly limited to the collapsed lower lobe; on the left it extends beyond the collapsed area, which does not appear to involve the whole lower lobe.

Discussion of Cases 1-5.—All these cases show the radiological picture of atelectatic bronchiectasis, a triangular opacity across the cardiophrenic angle on the right, or lying behind the heart shadow on the left side, within which bronchial dilatation is demonstrable by lipiodol injection. In the first two cases, bronchiectasis is limited to the collapsed area; in Cases 3 and 4 the two immediately adjacent bronchi also show some degree of dilatation, and in the fifth case there is not only atelectasis at both bases, but bronchiectasis extends considerably beyond the collapsed area on the left

side. The question whether the triangular opacities represent collapse of the whole of the lower lobe of the lung or of an accessory lobe will be considered subsequently.

Although the series is small, the similarity of the histories and clinical findings in these cases is sufficiently striking to justify certain generalizations.

ONSET AND SYMPTOMS.—In every case the information was volunteered that symptoms dated from an attack of pneumonia (probably broncho-pneumonia) in infancy or early childhood; in two cases this followed measles, and in one pertussis. In only one case was there a previous history of bronchitis. The presenting symptom has in every case been cough, which, while sometimes troublesome, has not been such as to cause any real disability or interference with normal activity. The complete absence of fœtid sputum and the infrequency of sputum of any kind has been very striking throughout the time that these children have been under observation. Sputum is, of course, liable to be swallowed in early childhood, but these patients are now at an age when it can be raised easily if present in considerable amount. Postural drainage has also proved unproductive. There is, in fact, nothing to indicate an anærobic infection of the bronchi of the type which produces the characteristic fœtid ' bronchiectatic ' sputum, although one child has shown some fœtor of the breath.

Similarly, constitutional disturbances have been very slight; the children have all had moderately good general health, and have gained weight steadily. Only in Case 2 is the patient considerably underweight for age. A second attack of pneumonia occurred in Case 3, but recovery was uneventful. Night sweats were complained of in Case 5, but were unaccompanied by pyrexia, and did not occur while the boy was under observation in hospital. Case 5 showed some constitutional disturbance after lipiodol injection, and subsequently developed acute hæmorrhagic nephritis. It is possible that the procedure lighted up some latent infection in the lung, but it did not result in any permanent increase in pulmonary symptoms.

The chronicity of the condition is as follows:—

	Present age.	Age at which pneumonia occurred.	Duration of symptoms.	Period of hospital observation.
Case 1	8 years	3 years	5 years	$3\frac{1}{2}$ years
Case 2	$9\frac{1}{2}$,,	$3\frac{1}{2}$,,	6 ,,	4 ,,
Case 3	9 ,,	5 ,,	4 ,,	4 ,,
Case 4	$13\frac{1}{4}$,,	$4\frac{1}{2}$,,	9 ,,	6 ,,
Case 5	$9\frac{1}{2}$,,	8 months	9 ,,	4 ,,

During the periods of observation, no significant changes have taken place in the severity of symptoms or in the physical signs, and it appears reasonable to suppose that bronchial dilatation is of relatively long standing in every case, although only recently demonstrated by lipiodol injection.

PHYSICAL SIGNS.—As already indicated, the children are moderately well-developed, and with one exception are not much under the average weight

for age. Examination of the chest in these long-standing cases usually shows little or no deformity or diminution of movement on the affected side. The percussion note is normal, or slightly impaired at the base posteriorly. Air-entry appears almost equal on the two sides. In two cases there was tubular (changing in one to amphoric) breathing heard over the affected area posteriorly. Indeed, the only physical sign occurring consistently was the presence of râles or crepitations at the base on the affected side. The heart was normal in position or only slightly displaced in four cases, and markedly displaced towards the affected side in one.

Clubbing of the fingers was present in four of the cases and absent in one; in three of the former it was noted for the first time over three years ago. The clubbing was in each instance relatively slight, a finding in keeping with the almost complete absence of toxæmic symptoms.

It is clear, therefore, that in cases of this type where the collapsed lung tissue occupies a small area in the paravertebral groove, diagnosis of the condition is not likely to be made on the physical signs alone.

These cases may be correctly described as examples of ' silent ' or ' dry ' bronchiectasis. As long as they remain in this stage, sputum is slight in amount or absent, there is little evidence of toxæmia, and the general health is good. It may be noted that hæmoptysis, a symptom occurring in many of the classical cases of ' dry ' bronchiectasis, has not occurred in any one of the present series. The clinical importance of the condition, however, lies in the fact which is exemplified in many of the reports of atelectatic bronchiectasis in older children and adults, that secondary infection of the dilated bronchi is always liable to occur.

It will also be seen that while the bronchiectasis may remain strictly limited to the atelectatic area, there is a tendency for the adjacent bronchi to become affected. This may well be a passive process, due not so much to infection as to the ' spilling-over ' of retained bronchial secretions which cannot readily be coughed out of the atelectatic area. These in turn will tend to clog the neighbouring bronchi, which, being situated next to an atelectatic area, themselves cannot be readily evacuated.

Reports of Cases 6-8, with comments.

As already indicated, investigation of chronic cases showing the characteristic triangular shadow in the radiogram almost invariably demonstrates an associated bronchiectasis within it, unless of course the shadow represents not atelectasis but the extremely rare condition of chronic mediastinal effusion. The following case (Case 6) illustrates the fact that where the collapse is an acute condition, and where the lung re-expands before the bronchial secretions have had opportunity to accumulate and stagnate within the atelectatic area, lipiodol injection may show no evidence of bronchial dilatation.

Case 6.—Collapse of the right lower lobe with re-expansion.

Case 6.—(Fig. 8 and 9) No. 31990.—J. F., a boy, aged 10½. Both parents and 5 other children are alive and well. The boy had diphtheria at the age of 3, and attended the children's out-patient department at the age of 8 with 6 months' history of cough with non-purulent sputum. No physical signs of disease were detected in the chest, and the general health was good; there was no clubbing. The patient was free from symptoms in two months, and was quite well until May, 1932 (aged 10). He was admitted to hospital under Professor Ellis on May 24th with 5 days' history of fever, cough, and pain in the left side of the neck. The patient had been kept in bed, and the cough had become more severe. On the day of admission the sputum was blood-stained.

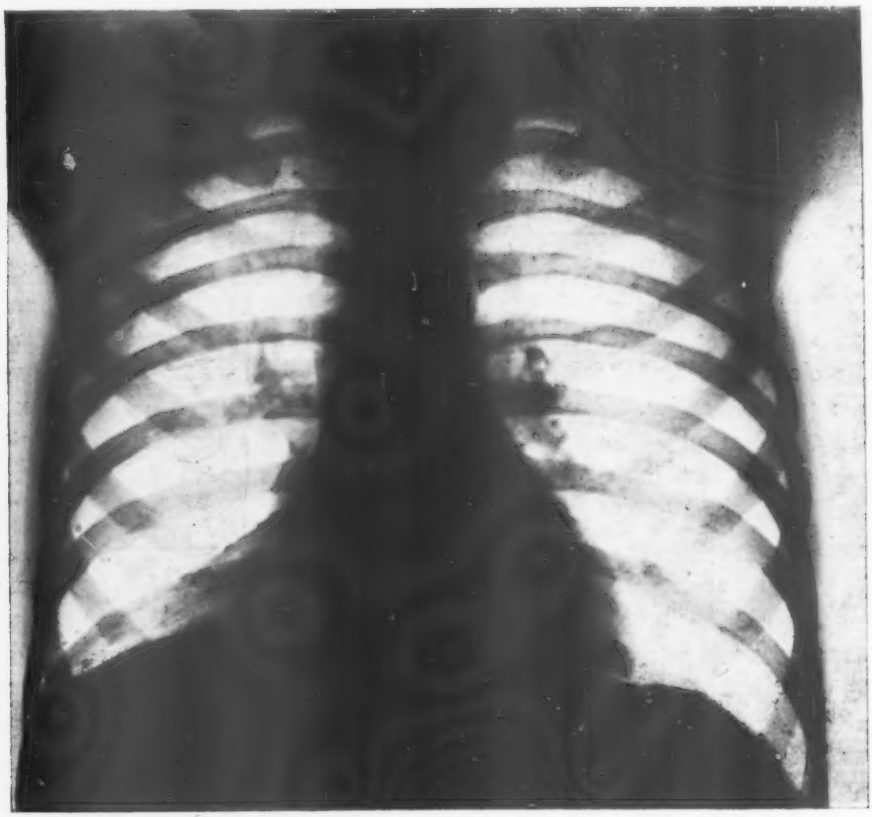

FIG. 8.—Case 6. J. F. Collapse of right lower lobe.

On examination: A well-developed and nourished boy, temperature 101°, respiration 36, pulse 136. There was no clubbing or cyanosis, but definite dyspnœa. The heart was not displaced. The chest showed diminished movement over the right lower lobe; the percussion note was dull over this area, and a pleural rub was heard in the right mid-axillary line at the level of the fourth rib. The breath sounds were tubular in character all over the right lower lobe, with ægophony at the right base posteriorly.

The case was diagnosed as right lower lobe pneumonia. The patient ran an irregular swinging temperature (to 104°) with morning rise and evening fall, finally settling on the 16th day of the illness. The chest was needled on the 10th day, but no fluid obtained. The physical signs in the chest persisted after the temperature had fallen to normal.

Radiological examination on June 21st (33 days after the onset of symptoms) showed a triangular shadow on the right across the cardiophrenic angle, indicating collapse of the right lower lobe.

In order to re-expand the collapsed lung tissue, the patient was treated by breathing exercises, consisting in blowing water from one bottle to another. A second radiological examination on June 30th showed the opacity still present in the right cardiophrenic angle, though less dense and tending to become less obvious on

FIG. 9.—Case 6. J. F. The right lower lobe which has re-expanded fills less well than the upper lobe, but the bronchial tree shows no abnormality.

deep inspiration, suggesting better æration. The opacity appeared smaller with the patient's back to the film, showing that the affected area was situated posteriorly.

An examination of the sputum for tubercle bacilli was negative.

The patient was discharged to convalescent home with some dullness and diminished air entry at the right base still present. He re-attended the out-patient department on his return 2 months later. He still had occasional cough with a small amount of sputum; there were râles scattered over the right lower lobe, and slight diminution of air entry, but the percussion note was unimpaired.

Radiological examination showed complete disappearance of the triangular shadow in the antero-posterior and lateral positions.

Lipiodol injection was carried out in December, 1932. The bronchi at the right base filled less well than the rest of the lung, but appeared normal. There was no evidence of bronchiectasis.

Two further cases (Cases 7 and 8) are included as illustrating primary causes of pulmonary collapse other than pneumonia in children, and because of their possible relationship to atelectatic bronchiectasis. It has not been

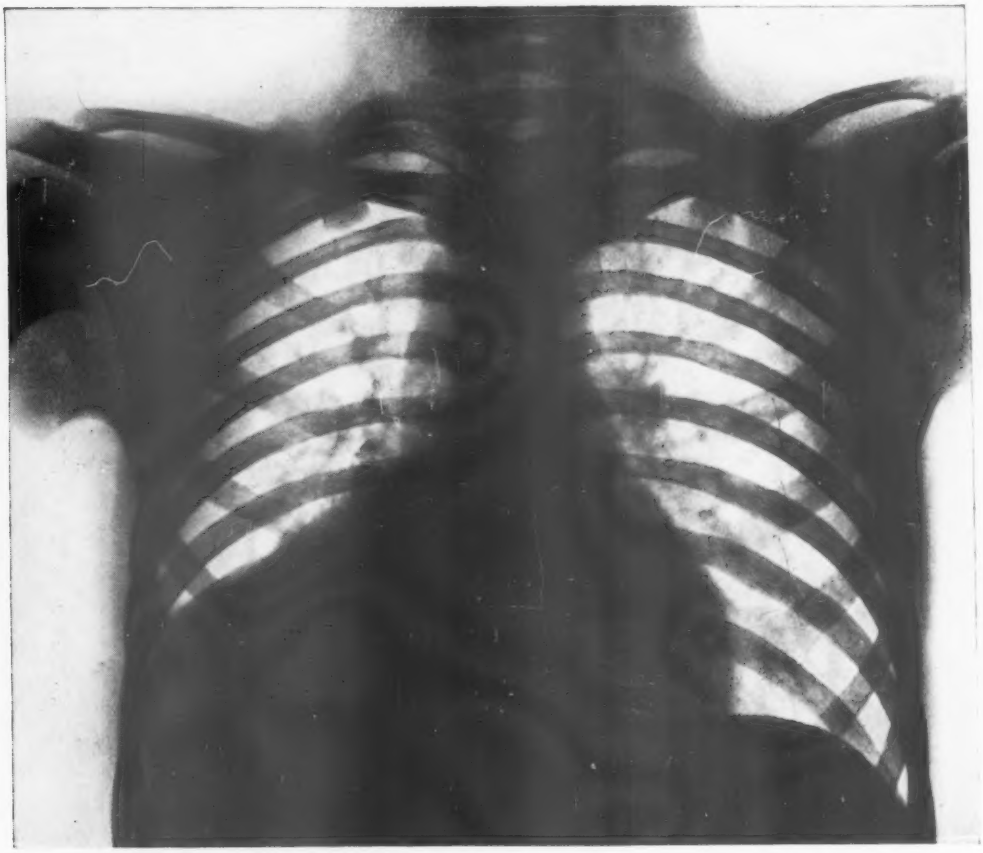

FIG. 10.—Case 7. B. R., May, 1931. Collapse of right lower lobe (triangular shadow in cardiophrenic angle), with raising of the right crus of the diaphragm, following inhalation of peanut.

possible to investigate the former by lipiodol injection, but from the persistence of cough and the X-ray appearance it is not improbable that bronchial dilatation either has occurred or is in process of developing.

Case 7.—Collapse of the right lower lobe, probably due to inhalation of a foreign body.

Case 7.— (Fig. 10 and 11) No. 30682.—B. R., a boy, aged 7½ years. Both parents and 1 brother are alive and well. There has been no tuberculosis in the family. The boy was well until February, 1931, aged 5 years and 8 months, when he had a sudden attack of violent coughing and dyspnœa while eating. He was put to bed, and the

cough and dyspnœa lasted for a week. A second attack of dyspnœa occurred in April, 1931, the spasm being such as to stimulate asthma, and there were 4 more similar attacks in the succeeding 5 weeks. The boy was admitted to hospital on May 7, 1931.

On examination (May, 1931): A well-developed and nourished Jewish boy; the respiration and temperature were normal while he was in hospital. There was no clubbing. The throat was clear. The apex-beat was in the 5th space 1 in. inside the mid-clavicular line. The left lung appeared normal; the right chest showed

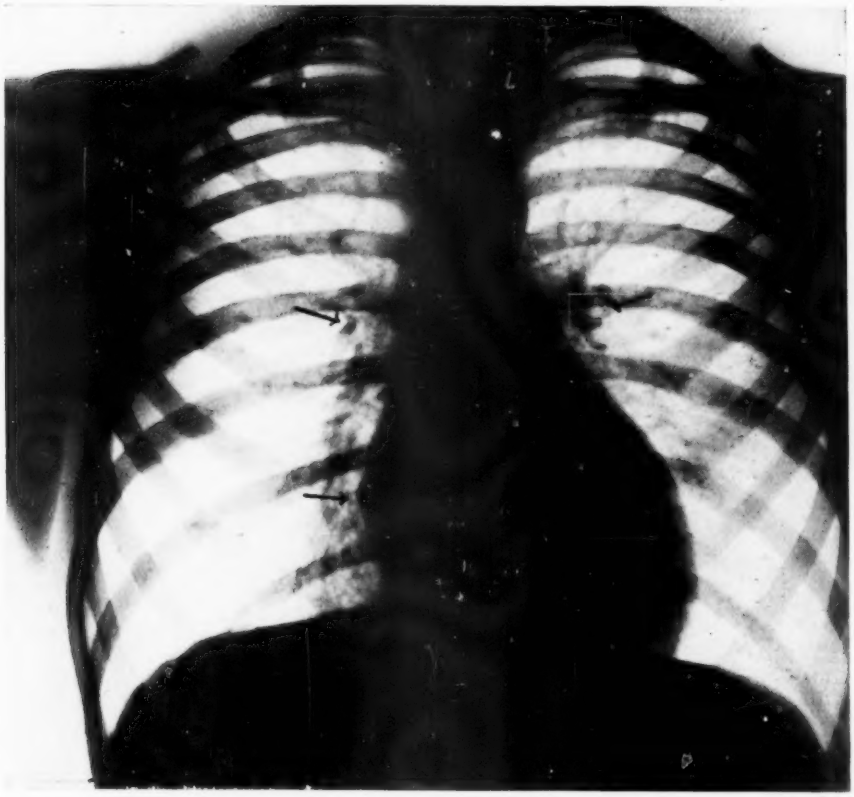

FIG. 11.—Case 7. B. R., June, 1932. The right lower lobe has re-expanded, but there is an area of dense fibrosis obscuring the right cardiophrenic angle. Several calcified glands are seen, and an area of infiltration in the left upper lobe.

diminished movement, and there was impairment of the percussion note in the right axilla and all over the right lung posteriorly, most marked over the lower lobe. The Mantoux test was negative (1 in 2,000 dilution). The right chest was needled posteriorly, but no fluid obtained.

Radiological examination showed the heart displaced slightly to the right, and a triangular shadow present in the cardiophrenic angle. The right diaphragm was raised.

The signs in the right chest persisted, and the boy was transferred to the Müller Convalescent Home, Broadstairs, where he has been until the present time under the care of Dr. H. M. Raven, to whom I am indebted for the subsequent history. The boy continued to have frequent cough and some respiratory spasm until October, 1931, when after a severe fit of coughing he produced what was thought to be a peanut. Since this time the cough has become much less frequent and severe (though

still present), and there has been no respiratory spasm. There is no sputum, and the breath is not offensive.

Radiological examination by Dr. C. J. Heaton, at the Margate General Hospital in June, 1932, showed that the dense triangular shadow across the right cardiophrenic angle had disappeared, but that there was heavy fibrosis along the ramifications of the right lower bronchus, and several small calcified glands at the cardiac margin on the right and around both hila. The right crus of the diaphragm was no longer abnormally raised. On the left side there was an appearance 'suggesting a resolving process (? tuberculous) in the upper lobe of the lung' (Fig. 11).

In this case (Case 7) acute collapse of the lung appears to have followed the inhalation of a foreign body, and re-expansion of the atelectatic lobe to have occurred when the foreign body was coughed up. It will be noted

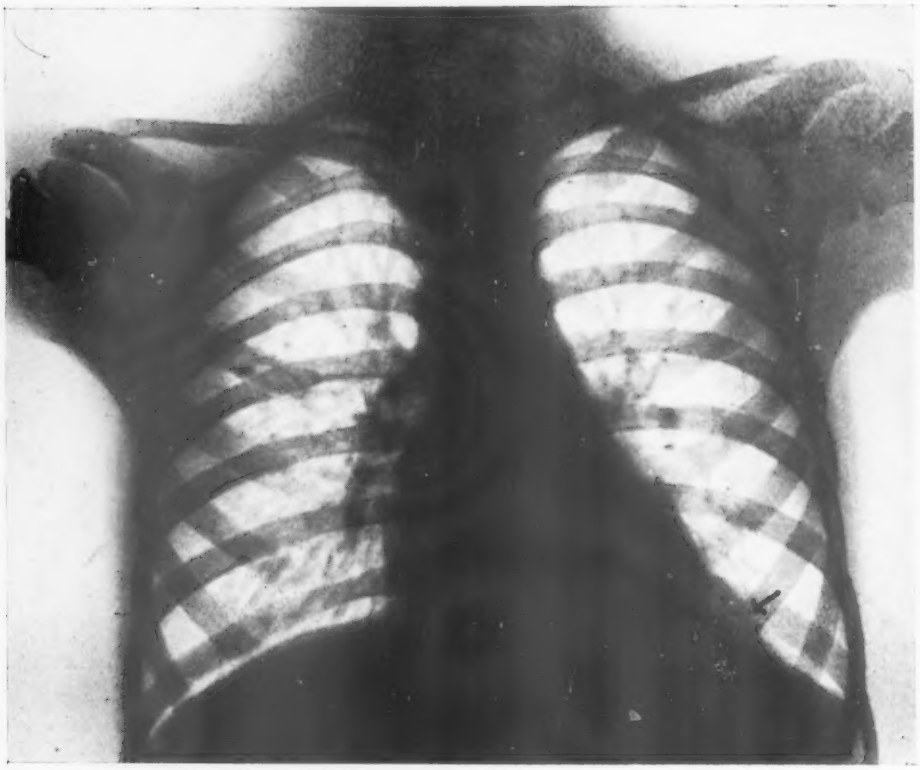

FIG. 12.—Case 8. V. H. Anterior-posterior view, showing tuberculous focus in right middle zone; the collapsed left lower lobe is almost entirely obscured by the heart shadow.

that when the child was first seen, the heart was displaced towards the side of the collapse, and the diaphragm raised on the same side. The fact that the second X-ray, taken a year after the foreign body had been coughed up, shows heavy fibrosis, with an appearance of streaking, across the right cardiophrenic angle, suggests that the lower lobe may not have been completely re-expanded and is the seat of fibrosis and possibly of bronchial dilatation. The picture is, however, complicated by the presence of several calcified glands at each hilum, which are not seen in the film taken in May, 1931.

Although the Mantoux test was negative in a dilution of 1 in 2,000 in 1931, the possibility of the present picture being due to chronic tuberculosis affecting a locus minoris resistentiæ cannot be excluded.

In the first five cases of typical atelectatic bronchiectasis, pulmonary tuberculosis has as far as possible been excluded by tuberculin tests or sputum examination. The fact that pulmonary tuberculosis may, however, be associated with a closely similar radiological picture is illustrated by Case 8.

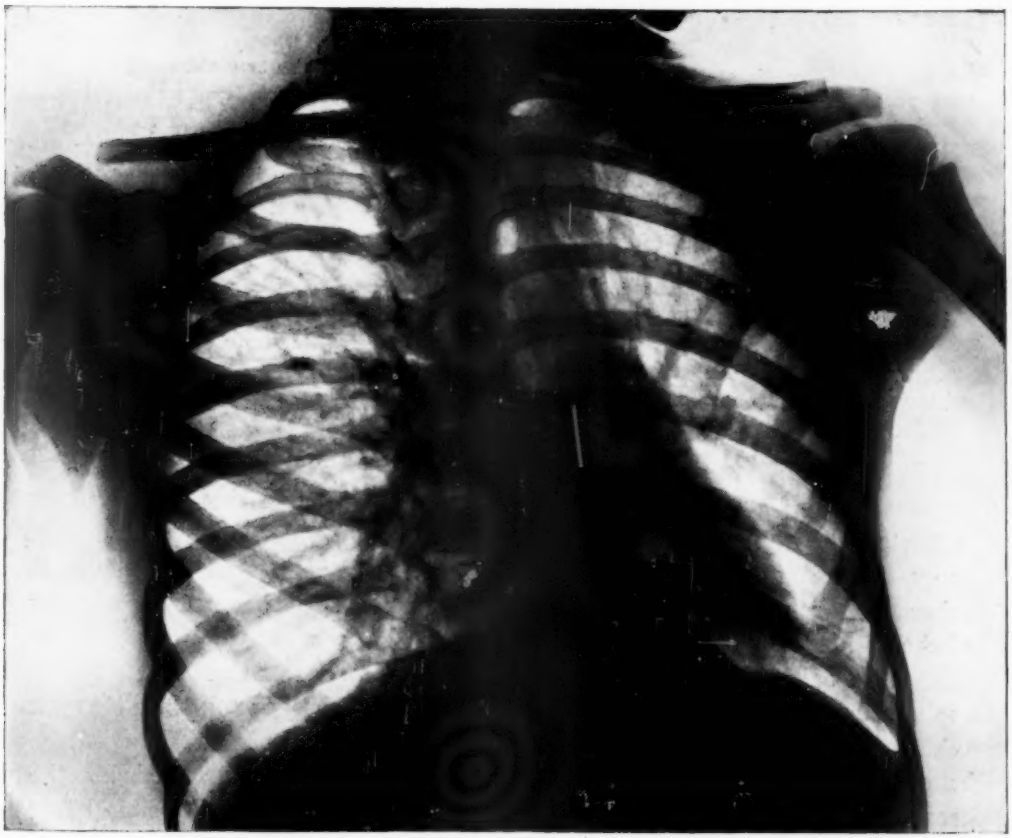

FIG. 13.—Case 8. V. H. Collapse of left lower lobe visible in semi-oblique position.

Case 8.—Pulmonary tuberculosis with collapse of the left lower lobe.

Case 8.—(Fig. 12 and 13) No. 41466.—V. H., a girl, aged 6½ years. Both parents are alive and well; 4 other children are alive and well, though one is said to have had pleurisy at the age of 8. There has been no known tuberculous contact. Except for measles during infancy, uncomplicated by pneumonia, there have been no acute illnesses though frequent feverish attacks; cough has been persistent since infancy. Until recently there has been little sputum, which was not purulent. At the age of 5½ years she was brought to hospital with a history of pains in left ankle for 2 years, and swelling of the joint for the past month. On examination, the joint was found to be swollen but not red or tender, with some limitation of extension and wasting of the muscles of the left calf. The chest was normally resonant, with equal air entry, but there were diffuse rhonchi throughout both lungs. Radiological

examination of the left ankle showed swelling and thickening of the synovial membrane, but no rarefaction or erosion of the bone. The Mantoux test was strongly positive in a dilution of 1 in 1,000. The joint was immobilized in plaster for 9 weeks, after which time the child was sent to a convalescent home. The cough and chest signs persisted throughout this time, and in April, 1932, at the age of 6, the sputum became increased in amount and was said to be foul on several occasions after severe attacks of coughing on waking. The child had several attacks of follicular tonsillitis during the spring and early summer of 1932, and her weight remained stationary. She was admitted to hospital in September.

On examination: A pale, moderately well-developed but poorly nourished child, weighing 38½ lb. (normal 41 lb.). The temperature, pulse and respiration were normal while she was in the ward, and cough was frequent. The left chest moved slightly less freely that the right, and the percussion note was impaired at the left base. There was no appreciable inequality of air entry on the two sides. The apex-beat was in the 5th space in the mid-clavicular line; the trachea was not displaced. The tonsils were small and cryptic and the nodes palpable. There was no clubbing of the fingers.

Radiological report: The diaphragmatic movements are not restricted. Lungs: calcified nodes in right middle zone and at left hilum. There is general relative loss of translucency over the right lung with pleural involvement and streaking in zone 1. Collapsed left lower lobe seen behind the heart shadow in left semi-oblique position.

Lipiodol injection showed poor filling of the collapsed area, but sufficient oil entered the left lower lobe to show several areas of dilatation or cavitation.

The patient was unable to raise any sputum while in hospital, but stomach-washings injected into a guinea-pig gave rise to typical tuberculous lesions in which tubercle bacilli were demonstrable.

The child was transferred for sanatorium treatment.

In this case it is significant that there is no previous history of broncho-pneumonia, and the collapse of the left lower lobe has presumably occurred in the course of an active tuberculous infection. The X-ray appearance is suggestive of a focus in the right middle zone, and it is possible that tuberculous sputum has been inhaled from this area and has caused blocking of the left lower lobe bronchus with resultant collapse. The pressure of an enlarged mediastinal gland on the left lower bronchus is another possible explanation. The collapsed area filled poorly with lipiodol, but there is evidence of either bronchial dilatation or cavitation within it. It will also be noticed that the collapsed lobe is almost entirely obscured by the heart shadow in the anterior-posterior view (the small portion visible being indicated with an arrow), but is well seen in the left semi-oblique position. It illustrates the fact that collapse of the left lower lobe may easily be overlooked unless the possibility of its occurrence is specially kept in mind. In order to demonstrate its presence in the anterior-posterior view, an X-ray of increased penetration is frequently necessary.

General discussion.

The conclusion that the triangular shadow already described represents an area of atelectasis, or rather collapse of a complete lobe, is based partly on direct inspection of the area involved post mortem or in the course of open operation, and partly on the configuration of the bronchi. Additional evidence is furnished by such cases as those described by Bezançon et al.[11]

and Sparks[5] where the shadow has disappeared, presumably due to re-inflation of the lung, although the bronchiectasis is of relatively long standing. Re-expansion and disappearance of a similar shadow is well seen in a case described by Findlay[12] and in Case 6 of the present series, where the collapse was of recent origin and unassociated with bronchiectasis. In the former, re-expansion was effected by inhalation of CO_2 and in the latter by breathing exercises. The manner in which disappearance occurred is in both cases much more in favour of the shadow representing collapsed lung than fluid effusion.

Open operation has been carried out on a number of the reported cases, and the appearance of the lung somewhat differently interpreted. As already mentioned, Rist et al.[3] described a case where operation showed an ' adhesive pleurisy ' instead of the mediastinal effusion for which search was being made; Sergent and Bordet[2] recorded induration of the parenchyma of the posterior border of the lung in a somewhat similar case. Singer and Graham[13], however, state emphatically that operation having been carried out on a considerably larger number of such cases ' these triangular shadows have been found to represent atelectatic, bronchiectatic lower lobes, with the characteristic cyanotic appearance and indurated feeling on palpation. . . . The unaffected lobe or lobes had hypertrophied so much as to fill out the chest cavity and surround the collapsed lobe.' Their findings do not suggest that the lobes affected were accessory lobes, though this view has recently been urged by Kerley[10], who regards the collapse as due primarily to lack of mechanical support in a lobe supplied by a para-cardiac branch of the lower lobe bronchus, which contains insufficient cartilage to keep the tubes patent.

In the single post-mortem specimen from a case of this type which I have had the opportunity of seeing, the collapsed area behind the heart involved the whole of the left lower lobe. The left upper lobe had expanded to fill the remainder of the left chest, and it is significant that while the left upper lobe happened in this case to be the site of a long-standing unresolved pneumonia, the collapsed lower lobe did not appear to be involved in the same pneumonic consolidation. There was very considerable peribronchial fibrosis in the atelectatic area, bronchiectasis, and a small amount of pus present in the larger cavities. While there was disorganization of the cartilage in the walls of the dilated bronchi, it appeared probable that this was secondary, due to erosion, rather than a primary absence of cartilage causing collapse. Indeed, the undilated bronchi were normally patent. There was some thickening of the pleura over the lower lobe, but this was considerably less marked than at the apex.

The lipiodol plates in the present series of cases also support the view that the whole lower lobe is affected, as the collapsed area is supplied from the first division of the main bronchus, while the bronchial tree in the upper lobe or lobes is spread out fan-wise from compensatory over-expansion and emphysema. This is well illustrated in Fig. 1 and 3,

The question whether the bronchiectasis preceded the atelectasis or vice versa, is one which it is difficult to answer with any certainty. It has been widely held that collapse will tend to occur around a bronchiectatic area, and that chronic infection of the lung parenchyma and fibrosis will tend to maintain it. Many of the cases give a history of broncho-pneumonia in infancy, from which period the symptoms have dated. A case reported by Bezançon et al.[11] might perhaps be quoted in support of this view, as the triangular shadow was seen to appear suddenly during an infective exacerbation of a bronchiectasis dating back to infancy.

On the other hand, it has been pointed out by Kerley[10] that there is considerable evidence against this view. Purulent sputum, wasting, and evidence of toxæmia are often absent until long after the diagnosis of bronchial dilatation is established, and cough is not necessarily persistent or severe. This suggests that the bronchial dilatation is at first a non-infective condition due to retention of bronchial secretions within a collapsed area, and as has been shown in many reported cases the typical clinical picture of bronchiectasis does not develop until secondary infection of the dilated bronchi takes place. It might reasonably be said that none of the five typical cases in the present series show clinical evidence of active infection of the bronchiectatic areas. It is not proposed to discuss the mechanism of collapse of the lung, but it is well established that collapse of a lobe, particularly a lower lobe, may follow the inhalation of a foreign body, as probably occurred in Case 7, or result from a pneumonia. In the absence of definite proof we are inclined to think that the usual sequence of events is as follows: Collapse of one or both lower lobes, and failure to re-expand, following broncho-pneumonia in infancy results in retention of bronchial secretions and bronchial dilatation. The presence of râles in every case makes such a retention of secretions appear probable, although the condition is relatively ' dry ' in comparison with the type of bronchiectasis showing abundant sputum. Secondary infection may not occur for many years, and during this period constitutional symptoms will be little in evidence, cough will not be frequent or productive, and what sputum there may be will not be fœtid. In rare cases, even when the bronchiectatic condition is of long-standing, re-expansion of the lung may take place with amelioration of symptoms (Bezançon et al.[11], Sparks[5]), but in general it may be said that the longer the condition has lasted the less likely is this to occur. This is comprehensible when it is considered that even in the absence of active bronchial infection there will almost inevitably be some degree of fibrosis of the atelectatic lung in the course of time, and it is even possible that the phrenic nerve may become nipped by fibrous tissue with resulting partial paralysis of the diaphragm. This latter eventuality would tend to maintain a condition of collapse.

Secondary infection when it occurs (and this may be relatively early or not until middle life) is likely to result in the rapid appearance of constitutional symptoms and render the prognosis extremely bad. The short

expectation of life which is usually allowed in bronchiectasis in childhood is due in part to the non-recognition of cases of this type. Not only is the characteristic shadow likely to be overlooked when it is obscured by the heart shadow, as is generally the case, many more examples occurring on the left side than on the right, but many of the children will not come under observation, owing to the absence of symptoms, until secondary infection has occurred.

From the point of view of diagnosis it may be said that whenever this X-ray appearance is seen and is of long-standing, bronchiectasis is almost invariably present, although there may be little to indicate it in the way of symptoms or physical signs; confirmation should be obtained by lipiodol injection.

Treatment.—Treatment is essentially preventive. No case of pneumonia with persistent cough or signs in the chest should be discharged before pulmonary collapse has been excluded by X-ray examination. If evidence of this is found, every effort should be made to re-expand the collapsed lobe by CO_2 inhalations or breathing exercises. When the condition is of long-standing, however, it is extremely improbable, though not impossible, that benefit will be obtained from these methods, and attention must be concentrated on preventing secondary infection and attention to the general health. Postural drainage should be tried, but is not likely to be effective. A long convalescence, and if possible a country life or open-air school are probably the most important lines of treatment during childhood. We have seen temporary benefit from repeated bronchoscopy and aspiration in a case where secondary infection had occurred, but it is doubtful if it should be advised in the uncomplicated case. In the same way, when the bronchiectasis is strictly limited to one lower lobe, it would seem logical to perform lobectomy. Unfortunately the operation is one with a high mortality in childhood, and cannot at present be advocated in cases where the symptoms are slight and the general health good. It would seem best to make every effort to prevent secondary infection until the child has reached an age when operation can be better supported.

Antiseptic inhalants are unlikely to be of any value, except in cases where the bronchiectasis has spread to the surrounding bronchi, as they will not enter the collapsed area to any appreciable extent. It is possible that lipiodol injection may be of real benefit where satisfactory filling of the whole area involved takes place, since the heavy oil will tend to displace the stagnant secretion from the dilated bronchi, allowing it to be coughed up. It is said that lipiodol may even remain in the cavities for many weeks; this has not, however, been confirmed in any of the cases of the present series that have been examined four or more weeks after its injection, although sometimes lipiodol has still been visible in the alveoli of the unaffected lobes.

Summary.

1. From a clinical consideration of five cases of atelectatic bronchiectasis in childhood, it is seen that the condition may exist, probably

for long periods, without the classical features of bronchiectasis such as fœtid sputum and evidence of toxæmia.

2. The view is held that bronchial dilatation occurs in these cases secondarily to collapse of the lower lobe of the right or left lung, with retention of bronchial secretion. Extension of the process may occur from spilling-over of retained secretion into the adjacent bronchi.

3. Collapse of one lower lobe probably occurs most frequently as a result of, or coincident with, broncho-pneumonia in early childhood, but the possibility of either inhalation of a foreign body or of pulmonary tuberculosis being responsible in certain cases is also considered.

4. Treatment should be directed to the re-expansion of the collapsed lung tissue in the early stages, and to prevention of secondary infection when fibrosis has occurred. It is doubtful if lobectomy is as yet advisable for cases of this type in childhood.

I wish to express my thanks to Dr. A. G. Maitland-Jones and Dr. K. H. Tallerman for providing facilities for investigating and reporting cases attending the Children's Department of the hospital, and to Professor A. W. Ellis for permission to include details of Case 6 which was admitted under his care; also to Dr. L. J. Rae, Honorary Assistant to the Radiological Department, for much help and co-operation and for most of the radiological reports.

REFERENCES.

1. Dieulafoy, G., *Manuel de Pathol. interne*, Paris, I, 1911.
2. Sergent, E., & Bordet, F., *Bull. et mém. Soc. méd. d. hôp. de Paris*, Paris, 1927, LI, 742.
3. Rist, E., Jacob, P., & Soulas, A., *Ibid.*, 1927, LI, 724.
4. Rist, E., Jacob, P., & Trocmé, P., *Ann. de méd.*, Paris, 1927, XXI, 144.
5. Sparks, J. V., *Brit. J. Radiol.*, London, 1931, IV, 30.
6. Pinchin, A. J. S., & Morlock, H. V., *Brit. Med. J.*, London, 1930, i, 12.
7. Ellis, R. W. B., *Proc. Roy. Soc. Med.*, London, 1932, XXV, 1734.
8. Rodgers, T. S., *Ibid.*, 1932-3, XXVI, 155.
9. Moll, H. H., *Quart. J. Med.*, Oxford, 1932, I, 457.
10. Kerley, P., *Brit. J. Radiol.*, London, 1932, V, 234.
11. Bezançon, F., & others, *Bull. et mém. Soc. méd. d. hôp. de Paris*, Paris, 1929, LIII, 1441.
12. Findlay, L., *Proc. Roy. Soc. Med.*, London, 1932, XXV, 407.
13. Singer, J. J., & Graham, E. A., *Am. J. Radiol.*, N.Y., 1926, XV, 54.

KETOGENIC DIET IN THE TREATMENT OF PYURIA IN CHILDHOOD*

BY

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In October, 1931, Helmholtz[1] published results of the treatment of pyuria in children by means of the ketogenic diet. This form of treatment was suggested to him by the observation that the urine of a patient being treated for epilepsy by ketogenic diet remained free of bacterial cloudiness after being kept for a week. He quotes Neilson[2], who in 1920 gave cream to patients with urinary infection and claimed good results due to increased acidity of the urine. In spite of previous in vitro experiments showing that the colon bacillus can grow in a medium of an acidity of pH 5·0 Nielson stated that in the absence of obstruction mere inhibition of growth is sufficient to cure a urinary infection. Even before this Shohl and Janney[3] in 1917 reported that the growth of bacillus coli was inhibited in urine of a pH of 4·6.

At the same time and from the same clinic, Clark[4] reported a series of adult cases of urinary infection treated by ketogenic diet with good results.

Helmholtz postulates two conditions which must be fulfilled for the effective employment of this mode of treatment. First, there must be a state of ketosis induced; and secondly, the urinary pH must be below 5·6. In a test series of four normal cases ammonium chloride was given, resulting in a urinary pH varying from 4·8 to 5·3. The growth of micro-organisms after inoculation and incubation of the urine of these patients was abundant. Again, in a test series of normal cases on ketogenic diet only those urines with pH 5·6 or below were rendered sterile after inoculation with micro-organisms and incubation. Ketosis was present.

More recently Wilson[5] was completely successful in treating himself with ketogenic diet for a urinary infection which had lasted seven months.

Present investigations

The object of this communcation is to report the results of this form of treatment in a series of six cases. Each patient was investigated on admission with regard to renal function by the ability to excrete phenolsulphonephthalein and to concentrate urea. The non-protein nitrogen of the blood was estimated and intravenous pyelography performed. The patients were then started on the ketogenic diet which was constructed by use of the formula

$$\frac{\text{Ketogenic units (K)}}{\text{Anti-ketogenic units (A.K.)}} = \frac{\text{Fat} + \frac{1}{2}\text{ Protein}}{\text{Carbohydrate} + \frac{1}{2}\text{ Protein}}$$

* The work was carried out during the tenure of a Carnegie Research Scholarship.

Table 1 shows the method of recording the daily observations. The first diet (A) was constructed to have K : AK ratio of 2 : 1 and this was steadily increased to 5 : 1 (Diet D) or even 6 : 1. Actually details of the diet are omitted for the sake of brevity but a diet of this nature can be easily constructed by reference to tables. Twenty-four hour specimens of urine, kept under oil, were examined in the side-room of the ward, Universal indicator being used for estimation of pH and Rothera's test for acetone. The duration of the course varied from 14 to 22 days. Cultures of the urine were made on the first and last days of the treatment.

Table 2 gives a summary of the results. Clinical details and results of the renal function tests are to be found in the summaries of the case reports. The acidity and ketonuria were considered to be satisfactory if the pH was 5·5 or lower and a very definite reaction to Rothera's test was obtained.

Results.—Four of the six cases had sterile urine free from pus at the end of the period of dietetic treatment. Cases 1 and 2 appeared to be cured, their urine being sterile one month after treatment had ceased, but Case 3 relapsed one week after the diet was stopped and Case 4 two weeks after. Case 5 was improved, there being no pus present in the urine and only a slight growth on culture, but a week after cessation of diet relapse occurred. In the sixth case, the urine was quite unaffected by the diet.

From these results it seems allowable to conclude that a state of ketosis accompanied by a highly acid urine does render the urine bactericidal, but that relapse is prone to occur. It is interesting to note that in each case in which relapse occurred some abnormality in the pyelogram was found. In these cases the urine became temporarily sterilized, but when treatment was stopped, either reinfection occurred, or a latent focus of infection became active once more.

Discussion.

In these six cases renal function tests all showed a poor result. In Case 5 where renal function tests had been performed in 1931, the lapse of a year showed a very considerable fall in the percentage excretion of phenolsulphonephthalein and in concentration of urea. Of all the patients this child showed the worst renal function, and it is interesting to note that the response to ketogenic diet was very poor both as regards acetonuria and acidity. Clark suggests that in a patient with diminished renal function the kidney is unable to excrete a urine of a low pH. He quotes a case of unilateral hydronephrosis in which urine from the normal kidney had pH 5·0, that from the affected one pH 7·0. In Case 6 renal function was also diminished, but had not reached the low level of Case 5.

By intravenous pyelography with uroselectan B an abnormality of the urinary tract was demonstrated in three of the uncured cases (Cases 3, 5 and 6). One or both kidney pelves were dilated with clubbing of the calices. In Case 4 the picture suggests an early deformity of the right renal pelvis. In contra-distinction, the two patients whose urines remained sterile and

TABLE 1.

CASE 4: A. M., FEMALE, 11½ YEARS.

Date	Diet	K Units	AK Units	Fat grm.	CHO grm.	Prot. grm.	Daily cal. intake	Urine			Remarks
								pH	Ketone bodies	Pus	
16–17 Oct.	A	94	47	80	32	29	960	7·5	Tr.	+	
17–18 ,,	B	110	37	97	24·5	26	1087	6·5	Tr.	+	$CaCl_2$ grm. xv 4x daily
18–19 ,,	C	133	35	120	23	25	1282	4·5	+	+	
19–20 ,,	D	150	32	137	18·5	27	1415	4·5	+ +	—	
20–21 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	+ +	—	
21–22 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	+ +	—	
22–23 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	— +	—	
23–24 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	+	— +	
24–25 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	+ +	— +	
25–26 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	+ +	—	
26–27 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	+ +	—	
27–28 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	+ +	—	
28–29 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	— +	—	
29–30 ,,	,,	,,	,,	,,	,,	,,	,,	4·5	— +	—	Culture sterile. No pus

TABLE 2.

Case	Age Years	Duration of illness. Years	No. of days on ketogenic diet	Acidity and ketonuria	Results		Remarks
					Immediate	After 1 week	
1	2	6/52	16	Poor	Pus — Culture —	Pus — Culture —	Pyelogram normal
2	8	2/12	15	Satisfactory	Pus — Culture —	Pus — Culture —	Pyelogram normal
3	7½	7/12	22	Satisfactory	Pus — Culture —	Pus + Culture +	Pyelogram abnormal
4	11½	1	14	Satisfactory	Pus — Culture —	Pus — Culture —	Pyelogram ? abnormal Relapsed after 2 weeks
5	11	3½	15	Very poor	Pus — Culture — +	Pus + Culture +	Pyelogram abnormal NH_4Cl for 2 days; vomited, discontinued
6	12	1,1/12	15	Satisfactory	Pus + + + Culture +	Pus + + + Culture +	Pyelogram abnormal

free from pus one month after the cessation of treatment, showed no abnormality on intravenous pyelography.

Neale[6] contends that chronic non-tuberculous pyuria is nearly always associated with deformity of the urinary tract. Of 56 cases which he followed up, 7 with persistent pyuria had also a deformity of the urinary tract. The above observations are in agreement with this, as the two patients who recovered on ketogenic diet had a relatively short history of infection and showed no X-ray evidence of abnormality of the urinary tract. Again in an investigation of cases of pyuria admitted to the Royal Hospital for Sick Children in the years 1920–1930, most of whom were under Professor Leonard Findlay's care, of a total of 435 admissions to hospital, only 7 over the age of 3 years died. In 6 of these cases abnormality of the urinary tract was demonstrated, in 5 at autopsy and in 1 at operation. In the seventh case no post-mortem examination was allowed.

If no abnormality is present ketogenic diet is probably an efficient method of clearing up a urinary infection, but it is questionable if it has any advantage over the older forms of treatment. Its use would appear to be limited to older children. In the acute stage of the disease when fever is present it seems unwise to give a diet so deficient in carbohydrate. Further, the diet can only be used satisfactorily in hospital, and even there co-operation on the part of the patient is required. The diet is unpleasant and, as in treating epilepsy, considerable difficulty is encountered when the higher K : AK ratios are given.

Summary

1. Six cases of chronic pyogenic infection of the urinary tract were treated with ketogenic diet.

2. At the end of treatment the urine was sterile in four cases and growth on culture scanty in a fifth, but three relapsed within three weeks. The sixth case showed no change in the condition.

3. In the two cases who were permanently cured the duration of the disease was short and no abnormality of the urinary tract was observed. In each of the four cases in which treatment failed abnormality of the urinary tract was demonstrated by pyelography.

4. It would appear that ketogenic diet is of little value as a curative agent in pyuria associated with abnormality of the urinary tract.

I wish to acknowledge my indebtedness to Dr. Stanley Graham who suggested this investigation and in whose wards the work was done.

REFERENCES.

1. Helmholtz, H. F., *Acta Pædiatrica*, Uppsala, 1932, XIII, 195; *J. Am. Med. Ass.*, Chicago, 1932, XCIX, 1305.
2. Nielson, O., *Ugesk. f. Laeger*, Copenhagen, 1920, XC, 843. Quoted by Helmholtz, H. F.[1]
3. Shohl, A. T., & Janney, J. H., *J. Urology*, Baltimore, 1917, I, 211.
4. Clark, A. L., *Lancet*, London, 1932, ii, 511.
5. Wilson, C. M., *Loc. cit.*, 960.
6. Neale, A. V., *Arch. Dis. Childh.*, London, 1931, VI, 164.

Appendix.

Summaries of case reports.

Case 1.—B. C., female, aged 2 years. B. coli infection of urinary tract of 3 weeks duration. Febrile on admission. Physical examination negative. Tuberculin skin reactions negative. Ketogenic diet started in sixth week of illness and continued for 16 days. The amount of acetone present in the urine and pH level varied considerably in spite of the addition of NH_4Cl grm. 15 every 4 hours. This was discontinued because of vomiting on the third day of administration. Urine at end of treatment was sterile and was still sterile 3 weeks later. Non-protein nitrogen 29·2 mgrm. per cent. Urea concentration test:—before urea, 2·02, first hour, 1·96, second hour, 1·20 per cent. Phenolsulphonephthalein excretion 34 per cent. in 2 hours. Intravenous pyelography showed no abnormality.

Case 2.—H. Y., female, aged 8 years. In hospital in 1931 with B. coli infection of urinary tract which cleared up on a course of injections of protosil into the bladder. Readmitted in October, 1932, with a staphylococcus albus infection of one month's duration. Ketogenic diet given for 15 days. Urine sterile at the end of treatment and still sterile 3 weeks later. Tuberculin skin reactions positive but no tubercle bacilli found on 2 examinations of the urine. Intravenous pyelography revealed no abnormality. Non-protein nitrogen 33·7 mgrm. per cent. Urea concentration test:—before urea 1·64, first hour 2·3, second hour 2·2 per cent. Phenolsulphonephthalein excretion 44 per cent. in 2 hours.

Case 3.—M. J., female, aged 7½ years. B. coli infection of the urinary tract of 7 months duration. Physical examination negative. Tuberculin skin reactions negative. Cystogram negative. Intravenous pyelography showed both kidney pelves and ureters to be dilated, the left more than the right. Ketogenic diet given for 14 days. Urine sterile at the end of treatment but relapse occurred a week later. Non-protein nitrogen 22 mgrm. per cent. Urea concentration test:—before urea 0·96, first hour 1·19, second hour 1·61 per cent. Phenolsulphonephthalein excretion 48 per cent. in two hours.

Case 4.—A. M., female, aged 11½ years. B. coli infection of 1 year's duration. Physical examination negative. Tuberculin skin reactions positive, but no tubercle bacilli found on 1 examination of the urine. Ketogenic diet given for 14 days with sterilization of the urine. Relapse occurred about 2 weeks later. Intravenous pyelograph showed doubtful early dilatation of right kidney pelvis and 1 calyx. Non-protein nitrogen 27 mgrm. per cent. Urea concentration test:—before urea 1·69, first hour 1·13, second hour 0·71 per cent. Phenolsulphonephthalein excretion 54 per cent. in two hours.

Case 5.—H. M., female, aged 10½ years. Pyuria diagnosed in 1929, since when she has been in hospital on 6 occasions. Physical examination negative. Tuberculin skin reactions positive, but examination of the urine for tubercle bacilli was negative on five occasions. Retrograde pyelography by Mr. Matthew White in 1930 showed clubbing of calices of the right kidney. In 1931 non-protein nitrogen was 31·5 mgrm. per cent. Urea concentration test:—before urea 1·64, first hour 1·66, second hour 1·86 per cent. Phenolsulphonephthalein excretion in two hours 62 per cent. Retrograde pyelography by Mr. Matthew White showed both kidney pelves and ureters to be dilated. In October, 1932, ketogenic diet was given for 16 days with improvement, there being no pus and only a slight growth on culture of the infective organism, a gram-negative cocco-bacillus. In this case pH of the urine was never below 6·5 and acetonuria was not marked. A week after diet was stopped relapse occurred. Non-protein nitrogen 43 mgrm. per cent. Urea concentration test:—before urea 0·87, first hour 0·84, second hour 0·88 per cent. Phenolsulphonephthalein excretion 8 per cent. in 2 hours.

Case 6.—I. D., female, aged 12 years. B. coli infection of urinary tract since January, 1931. Tuberculin skin reactions negative. Physical examination negative. Cystogram negative. Cystoscopic examination by Mr. Matthew White revealed a dilated bladder with marked cystitis and double ' golf hole ' ureter. Non-protein nitrogen 31 mgrm. per cent. Urea concentration test:—before urea 1·17, first hour 1·19, second hour 1·87 per cent. Phenolsulphonephthalein excretion 43 per cent. in 2 hours. In January, 1932, intravenous pyelography showed enlargement of right kidney pelvis and ureter. In October, 1932, ketogenic diet given for 16 days with no effect on the urine in spite of a constant low pH and adequate acetonuria. Non-protein nitrogen 35·5 mgrm. per cent. Urea concentration test:—before urea 0·97, first hour 1·35, second hour 1·28 per cent. Phenolsulphonephthalein excretion 43 per cent in 2 hours.

A CASE OF PAPILLOMA OF THE CHOROID PLEXUS

BY

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The following case appears to be worthy of publication owing to the unusual nature of the tumour. According to Cushing[1] the incidence of papilloma of the choroid plexus is not more than 0·5 per cent. of all cerebral tumours.

I am indebted to Dr. J. F. Ward for permission to make use of the clinical records of the following case which was under his care in the Royal Manchester Children's Hospital.

Case report.

A girl of 7 years was admitted to the Royal Manchester Children's Hospital under Dr. Ward's care on March 12th, 1932. The history was as follows. The child had recovered from measles 3 weeks previously, since when she had taken little interest in anybody. For a fortnight she had complained of headache and of cramp-like pain in the arms and legs, and for the same period nearly all food had been vomited. For 1 week control of the bladder and rectum had been lost.

Examination of the heart, lungs and abdomen did not reveal any abnormality. Examination of the nervous system revealed a rational but very slow cerebration. There were no paralyses and the superficial and deep reflexes were normal in response. The pupils were dilated but were equal in size and reacted to light and accommodation. There was slight nuchal rigidity, and Kernig reactions were obtained on both sides. There were no sensory changes.

Lumbar puncture was performed 3 times, but on no occasion did the cerebro-spinal fluid show any departure from normal.

The girl remained in hospital in a semi-comatose condition with frequent vomiting, and just before death on May 26th, 1932, she developed a bilateral optic atrophy.

A diagnosis of cerebral tumour was made but localization was impossible.

Post-mortem examination.—At autopsy the body was very emaciated. All the organs of the chest and abdomen, though nearly devoid of fatty tissue, were normal.

On opening the skull the meninges were found to be normal. The brain was removed and a rounded well-circumscribed tumour, 6·5 cm. in diameter, was found situated below the posterior two-thirds of the left cerebral hemisphere (Fig.1). There was also a tongue-like process of growth 1·5 cm. in length by 0.75 cm. in breadth, which passed through to the external surface of the hemisphere. The growth was somewhat lobulated on the surface and was seen to be of a deep reddish-brown colour.

On microscopical section it proved to be a typical papilloma with numerous cauliflower-like villi containing a central core of connective tissue covered with a single layer of cuboidal cells (Fig. 2).

The growth had evidently arisen from the choroid plexus of the third ventricle.

Discussion.

Incidence of cerebral tumours in general and of the choroid plexus papilloma in particular.—In discussing the incidence of cerebral tumours in

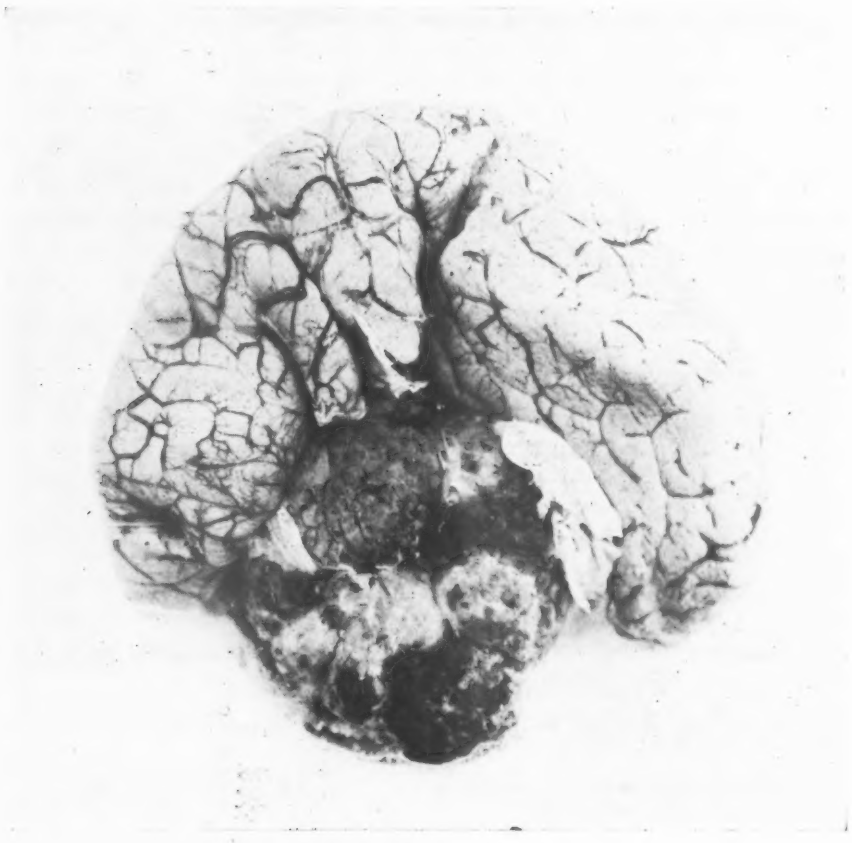

FIG. 1.—View of brain.

childhood, Leavitt[2] found 23 cases among 350 records of tumours in the Philadelphia Hospitals, but not a single case of papilloma of the choroid plexus was reported. These figures give a lower incidence than those of Cushing[3] who reported 154 from records of 1,108 cases; of these 154, 44 only were cerebral, 110 cerebellar. These figures give some idea of the comparative rarity of cerebral tumours in childhood.

von Wagenen[4] collected 45 cases of choroid plexus papilloma from the literature and reported 2 of his own. Of these, 6 were observed by Cushing[1]. I have been able to trace another 7 which with the above case makes a total of 55 reported cases, 6 of which were reported by Cushing[1] and 1 by Guillain and others[5].

Age incidence.—In the first decade of life there are 13 cases, in the second 6, and in the third and succeeding decades, 22. The age of 14 patients was not recorded. The youngest age was 3 months and the oldest 74 years.

Sex incidence.—The sex was so rarely mentioned that it is not possible to draw any conclusions as to the sex incidence.

FIG. 2.—Section of tumour.

Site of the tumour.—The site of these tumours is interesting. 16 occurred in the lateral ventricle, of which 11 were on the left side, and one occupied both ventricles. 10 occurred in the third ventricle, but the greater number (29) were found in the fourth ventricle.

Signs and symptoms.—Apart from the classical signs and symptoms of cerebral tumour (headache, vomiting and papillœdema) there seem to be but few aids to the diagnosis of choroid papillomata, although it is noticeable that some have been confused with acoustic tumours owing to the presence of deafness, nystagmus and disorders of equilibrium. Guillain[5] reports one such case and Cushing[1] mentions three others.

Conclusion.

In conclusion papillomata of the choroid plexus are rare tumours, 54 only having been previously described; they tend to be commoner in early life. Though they may be present in any of the ventricles the greater number have occurred in the fourth ventricle, and they may be mistaken for acoustic tumours.

I should like to thank Dr. J. F. Ward for kindly allowing me the use of his clinical notes.

REFERENCES.

1. Cushing, H., *Intracranial Tumours.*
2. Leavitt, F., *Am. J. Med. Sc.*, Philad., 1929, CLXXVIII, 229.
3. Cushing, H., *Am. J. Dis. Child.*, Chicago, 1927, XXXIII, 551.
4. von Wagenen, W. P., *Arch. Surg.*, Chicago, 1930, XX, 199.
5. Guillain, G., Petit-Dutaillis, D., & others; *Rév. neurol.*, Paris, 1932, XXXIX, i, 497.

THE HÆMOLYTIC STREPTOCOCCUS AS A FACTOR IN THE CAUSATION OF ACUTE RHEUMATISM

BY

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Introduction.—The conception of acute rheumatism as a manifestation of, or sequel to, infection with the hæmolytic streptococcus has lately received much support.

Coburn (1931) has put forward clinical, epidemiological and bacteriological evidence of the causal relationship of this micro-organism. Perhaps the most striking results which he records are those of skin reactions on rheumatic and non-rheumatic subjects in which he used ' nucleo-protein ' from a variety of bacteria. An association between infections of the upper respiratory tract and skin reactions to the homologous nucleo-protein could be demonstrated, and in cases of acute rheumatism the hæmolytic streptococcus appeared to be the important invader as judged by cutaneous allergy.

Previous to this Birkhaug (1927) and Kaiser (1928) had suggested infection with a well defined non-methæmoglobin-producing type of streptococcus as the cause of acute rheumatism and had applied skin-tests with filtrates of cultures of this organism. Irvine-Jones (1928), who noted similar skin reactions, was inclined to the view that streptococci were related to acute rheumatism though no one type of the micro-organism was incriminated. Mackenzie and Hanger (1927), on the other hand, after a study of allergic reactions to antigens of streptococci of different types could not correlate their findings with any previous or existing infections.

Schlesinger (1930) and others have recorded the frequent observation of acute nasopharyngeal infection, sometimes associated with hæmolytic streptococci, as having an apparently specific effect in activating latent rheumatism. Sheldon (1931) recorded an outbreak of epidemic relapse among rheumatic convalescents, the recrudescence of the rheumatic symptoms following tonsillitis after a latent period of one to three weeks. Of particular significance was his finding that febrile attacks following infection with other organisms (pneumococcus, B. influenzæ and M. catarrhalis) did not appear to influence the rheumatic state in any way. Collis (1931) proved that in this outbreak the throat infection preceding the relapse was due in all cases to the hæmolytic streptococcus and, on the lines of Coburn's work, showed a high percentage of rheumatic patients to be allergic when skin-tested with extracts of this micro-organism. Recently Todd (1932), approaching the problem from the immunological aspect, has shown that those suffering from acute rheumatism possess in their serum a higher concentration of anti-hæmolysin capable of neutralizing specifically the hæmolytic toxin of S. pyogenes than that in the serum of normal individuals. The presence of this anti-body is indirect evidence of previous infection with the hæmolytic streptococcus. A similar inference may be drawn from the results of Nicholls and Stainsby (1931) who demonstrated agglutinins for streptococci in a high proportion of cases of rheumatism. Suggestive results are reported in a recent paper by Collis and Sheldon (1932) who attempted desensitization of rheumatic

children by intravenous vaccination with hæmolytic streptococci. They found that in presence of a persistent focus of infection in the throat the vaccine stimulated an apparently specific focal reaction in the pericardium and joints while in the absence of such a focus considerable clinical improvement followed the vaccination. In a proportion of cases which had previously given a positive reaction to hæmolytic streptococcus extract the reaction became negative after the vaccine course.

Present investigations.

The work here recorded is a study of cases of acute rheumatism in Edinburgh along lines similar to those employed by Collis and Sheldon in London. With the co-operation of physicians of various institutions in the city, cases have been examined bacteriologically, full clinical data recorded, and intradermal tests with extracts of numerous strains of streptococci of all types carried out. An equal number of non-rheumatic controls of the same age and in the same wards have been investigated in the same way.

Throat swabs.—Throat swabs were inoculated on horse-blood-agar plates within two hours of being taken. After 24 hours' incubation hæmolytic colonies were subcultured on to a further blood-agar plate. Single colonies from the second plate were inoculated on to a heated-blood-agar plate for observation of methæmoglobin production. In the absence of this a single colony was again picked off and transferred to a tube of Robertson's cooked-meat medium with liquid paraffin seal. In this medium the micro-organisms gave a profuse growth after 24 hours and could be stored in the dark at −6° C. for months without subculture. This medium was selected for the maintenance of cultures in preference to blood-broth because it could be sterilized by autoclaving, thus avoiding the risk of contamination inseparable from any medium containing fresh body-fluids. In addition the anærobic conditions and infrequent subculture tend to preserve the virulence, and probably also the serological characters, of the strain as isolated.

In all cases the production of hæmolysin for the red corpuscles of the horse in broth culture was estimated quantitatively, and all strains excluded if no such lysin could be demonstrated.

Bacterial extracts.—Streptococci from which extracts were made were grown for 24 hours in phosphate broth, 100 c.cm. of broth in large centrifuge tubes being employed. The micro-organisms were centrifuged and the supernatant broth removed. The sediment was washed twice in 0·85 per cent. sterile saline solution and once in sterile water. The final sediment in approximately 1 c.cm. of water was transferred to the flask of a bacterial ball-mill and dried. At first the vacuum desiccator was used, but a product of exactly the same quality was found to result if the micro-organisms were dried in air at 45° C. for 18 hours. The dried micro-organisms were then ground by rotation of the mill for three days and two nights. The powder resulting was suspended in 10 c.cm. of sterile saline and heated at 60° C. for 15 mintues in a water-bath. Rapid centrifuging was then employed to separate the bacterial debris and the supernatant fluid, after the addition of 0·5 per cent. phenol, was concentrated extract (H.S.E.) for use, after dilution, in the skin-tests.

Standardization of extract preparations.—The nitrogen content of all extracts was estimated by the micro-Kjeldahl method, the results being shown in Table 1. As the dosage used throughout the tests was 0·2 c.cm. of a 1 in 100 dilution, the nitrogen content of each injection of the hæmolytic streptococcus preparation was 0·00028 mgrm. The comparable figure for the extracts used by Collis (1931) and Coburn (1931) was 0·0002 mgrm.

TABLE 1.

NITROGEN CONTENT OF VARIOUS EXTRACTS.

Type of streptococcus	N. content of undiluted extract
Hæmolytic streptococcus from throat of case of rheumatic fever	14 mgrm. per cent.
Hæmolytic streptococcus from throat of case of scarlet fever	22 ,, ,, ,,
Hæmolytic streptococcus from blood of case of puerperal fever	18 ,, ,, ,,
Hæmolytic streptococcus from throat of healthy person	16 ,, ,, ,,
Streptococcus viridans from throat of case of rheumatic fever	23 ,, ,, ,,
'Gamma' streptococcus from throat of case of rheumatic fever	12 ,, ,, ,,

By the courtesy of Dr. Collis we were able to carry out simultaneous tests with his extract and our own in a series of 49 rheumatic and 15 non-rheumatic cases. The results, which it is unnecessary to give in detail, showed that 75 per cent. of the rheumatic cases and 87 per cent. of the non-rheumatic cases gave identical reactions. In the remaining cases in both groups the differences were only of degree and very slight. In no case was the reaction to Collis' extract positive when that to our own was negative, or vice versa. Our results and his may, therefore, be considered comparable.

Intradermal tests.—The volume of the appropriate dilution (usually 1 in 100) of all extracts injected into the skin was 0·2 c.cm. A 1 c.cm. syringe and intradermal needle were used. In every patient at least 6 tests were made and 2 tests were done at one time, an interval of one day elapsing between each pair. Reagents used in the tests usually consisted of (1) and (2) extracts of different strains of hæmolytic streptococci, (3) extract of a viridans streptococcus, (4) extract of a 'gamma' streptococcus, (5) Dick toxin, (6) Dick 'control.'

Readings were made after 24 and 48 hours, two diameters at right angles being taken and also the diameter of the papular centre present in many of the more severe reactions. A note was also made of œdema and tenderness, if present, and the colour of the reaction.

As a rule only one set of observations was made on each patient, but when the duration of treatment in the ward permitted, the tests were all

repeated at monthly intervals. With each set of tests throat swabs were repeated.

Strains from which extracts have been prepared included the following:—

(1) Strain of hæmolytic streptococcus from throat of a case of acute rheumatism. This extract was standardized by parallel tests performed along with an extract supplied by Dr. Collis as described. It has been used throughout and extracts of other hæmolytic streptococci have been tested in comparison with it. In the following tables all the results tabulated under the heading H.S.E. (hæmolytic streptococcus extract) are those obtained with this extract.

(2) Strain of hæmolytic streptococcus from a normal control throat.

(3) Strain of hæmolytic streptococcus from an early case of scarlet fever. (This was serologically typed by Dr. F. Griffith and found to be type II.)

(4) Strain of hæmolytic streptococcus freshly isolated from blood-culture in a case of puerperal septicæmia.

(5) Strain of streptococcus viridans isolated from the throat in a case of acute rheumatism.

(6) Strain of ' gamma ' streptococcus isolated from the throat of a case of acute rheumatism. This strain was streptococcal in morphology, insoluble in bile and quite inert on fresh or heated blood-agar. It did not show the heat resistance (60° C.—15 minutes) associated with the enterococcus. Unlike Birkhaug's (1927) streptococcus it did not ferment inulin.

Dick toxin and control were the commercial preparations of Burroughs Wellcome and Company, Limited.

Results.

In all 140 cases of acute rheumatism have been examined, together with 145 controls chosen as being of the same age, sex and environment as the rheumatic cases. A complete investigation could not be made on all owing in a few instances to removal from the wards soon after tests were commenced. Again throat swabs were frequently taken in rheumatic out-patients on whom it was not possible to carry out skin-tests. In other cases in the early stages of the work the throat swabs of cases were not taken at the time of the tests. A further source of apparent discrepancy in the totals recorded in the tables is that in the later stages where the H.S.E. and Dick reactions were both positive, serum neutralization tests were done which replaced the reactions with viridans and ' gamma ' extract. These facts explain why the numbers appearing in the tables do not include the whole 140 cases and 145 controls. The results tabulated include all the data we have collected on each point in the investigation, and no selection of available material has been made for this report.

The skin reaction to extract of hæmolytic streptococci.—At the outset we were able to verify the findings of Coburn (1931), Collis (1931) and others, that the soluble products of ground streptococci produced a well-defined reaction when injected into the skin of certain individuals. Appearing in from 6 to 12 hours, an area of erythema gradually increased in size and attained its maximum in 36 hours, when it slowly faded. Swelling was present in all the more marked reactions, sometimes diffuse over the whole red area, but more usually concentrated in an area of 10 to 18 mm. diameter in the centre. This central papule was invariably tender and of a deeper red than the peripheral zone. The maximum diameter of the reaction varied enormously from the weak or doubtful positive of 12 mm. to a large area attaining a diameter of 120 mm. or more. General symptoms were not as a rule noted. In a group of medical students tested, a small number complained of headache, dizziness and in one case vomiting which appeared 4 hours after the test injections. Mackenzie and Hanger (1927) reported similar general reactions which were more frequent in adults than in children. Apart from this group of medical students, however, with perhaps one exception, such systemic disturbances were never detected.

TABLE 2.

EXTRACT OF HÆMOLYTIC STREPTOCOCCUS (FROM THROAT OF RHEUMATIC CASE): RESULTS OF INTRADERMAL REACTIONS IN 140 CASES OF ACUTE RHEUMATISM AND 145 CONTROLS.

Group	Total	Weak positive 12-19 mm. mean diameter		Strong positive Over 20 mm. mean diameter		Negative	
		Total	Percentage	Total	Percentage	Total	Percentage
Rheumatic	140	18	12	89	64	33	24
Control	145	31	20	50	35	64	45

Incidence of positive reactions in rheumatic and control groups.—Table 2 classifies the results of skin tests in rheumatic and control groups as weak positive, strong positive and negative. It will be noted that the most significant difference between the two groups was shown by the strong positive reactions where the rheumatic group showed a rate of 64 per cent. as compared with 35 per cent. in controls. It is noteworthy that the weaker reactions were more common in controls than in cases of rheumatism. The results we obtained were on the whole similar to those of Collis (1932) who showed that 25 per cent. of cases of rheumatism gave negative results to H.S.E. (as compared with our 24 per cent.), while 28 per cent. of non-rheumatic controls reacted strongly to the extract (as compared with 35 per cent. in our series). Extracts of other hæmolytic streptococci from cases

of scarlet fever, puerperal fever and normal control throats have been used in parallel with the extract of the rheumatic strain in a number of individuals. Except that some extracts were consistently rather stronger than others, there was a remarkable agreement among the results with hæmolytic strains. The skin-reacting factor appeared to be common to many if not all strains of hæmolytic streptococci.

It was noted that the positive skin reactions obtained in cases at one hospital (the Astley Ainslie Institution) were larger and more frequent than in the other hospitals. This institution for convalescents receives many old-standing ear, nose and throat cases of which many were doubtless of hæmolytic streptococcal origin. Table 3 indicates the results in the group

TABLE 3.

INCIDENCE OF POSITIVE REACTIONS AND SIZE OF REACTIONS IN RHEUMATIC AND CONTROL GROUPS COMPARED IN (A) A CONVALESCENT INSTITUTION, AND (B) ALL OTHER HOSPITALS WHERE PATIENTS WERE STUDIED.

Group	Convalescent institution			Other hospitals		
	Total	Percentage strongly positive to H.S.E.	Mean diameter of H.S.E. reaction	Total	Percentage strongly positive to H.S.E.	Mean diameter of H.S.E. reaction
Rheumatic	18	89	36·34 mm.	64	59	20·47 mm.
Control	21	81	31·29 mm.	110	31	13·29 mm.

of rheumatics and controls which were tested there, and for comparison the results obtained at other institutions over the same period of time are included. It will be seen that the proportion of positive reactors, 89 per cent. and 81 per cent. for rheumatic and control groups respectively, is much above the percentages recorded elsewhere (59 per cent. and 31 per cent.). In addition the severity of reactions, indicated by the mean diameter for all cases was much higher in the special convalescent hospital group. It will be seen that the percentage of positives and the mean diameter of reactions in the non-rheumatics of this institution are both greater than those in rheumatic cases elsewhere. The further significant fact was elicited that of the 16 cases of quiescent rheumatism in the Astley Ainslie Institution who gave strongly positive extract reactions, 8 were harbouring hæmolytic streptococci in the throat. No relapses occurred in these during three months of observation.

Streptococcus viridans has been associated with many theories of the ætiology of acute rheumatism. On the assumption that an allergic skin reaction to the extract of such a streptococcus might be an index of previous infection, all cases were tested as described with such an extract,

The results recorded in Table 4 show that no significant difference existed between the two groups in their reactions to this extract.

TABLE 4.

EXTRACT OF VIRIDANS STREPTOCOCCUS (FROM THROAT OF RHEUMATIC CASE): RESULTS OF INTRADERMAL REACTIONS IN 120 CASES OF ACUTE RHEUMATISM AND 131 CONTROLS.

Group	Total	Weak positive 12-19 mm. mean diameter		Strong positive Over 20 mm. mean diameter		Negative	
		Total	Percentage	Total	Percentage	Total	Percentage
Rheumatic	120	18	15	33	27	69	58
Control	131	27	21	32	24	72	55

Similarly in Table 5 are shown the results obtained with extract of 'gamma' type streptococcus. Especially significant in this case is the similarity between rheumatic and control groups in the percentage of negative reactions. The differentiation of weak from strong positive reactions is arbitrary, but of more significance is the sum of all reactions which shows no difference between the two groups.

TABLE 5.

EXTRACT OF INERT 'GAMMA' STREPTOCOCCUS: RESULTS OF INTRADERMAL REACTIONS IN 122 CASES OF ACUTE RHEUMATISM AND 131 CONTROLS.

Group	Total	Weak positive 12-19 mm. mean diameter		Strong positive Over 20 mm. mean diameter		Negative	
		Total	Percentage	Total	Percentage	Total	Percentage
Rheumatic	122	16	12	26	21	80	67
Control	131	24	18	22	17	85	65

While no apparent relationship could be established between the non-hæmolytic streptococci and acute rheumatism by the intradermal reaction, there was some evidence that allergic reactivity to H.S.E. was not entirely independent of that to the non-hæmolytic types.

All rheumatics and controls who had been tested simultaneously with extracts of all three types of streptococcus were grouped according to the intensity of reaction to H.S.E. (strong positive, weak positive and negative). It was then possible to determine the percentage of positive

reactors to extracts of viridans and ' gamma '-type streptococci respectively in each of these groups. Apart from its relationship to acute rheumatism, the presence of allergy to H.S.E. appeared to increase the probability of allergy to products of non-hæmolytic streptococci being present. Table 6 shows that in presence of a strongly positive reaction to H.S.E., 62 per cent. of all individuals (cases and controls) react to extract of S. viridans while only 17 per cent. of those failing to react to H.S.E. reacted to extract of S. viridans or ' gamma ' streptococci. The general tendency in both rheumatic and control groups is for the reactivity to the non-hæmolytic streptococcal extract to be less as the intensity of reaction to H.S.E. declines.

TABLE 6.

60 RHEUMATIC AND 80 CONTROL CASES GROUPED ACCORDING TO THE INTENSITY OF REACTION TO H.S.E. INCIDENCE OF POSITIVE REACTIONS TO EXTRACTS OF VIRIDANS AND ' GAMMA ' STREPTOCOCCI IN EACH GROUP.

		Percentage of strongly positive reactions to extracts of non-hæmolytic streptococci	
		Viridans type	' Gamma ' type
Group giving strong positive reactions to H.S.E. (over 20 mm.)	Rheumatics (39)	67 per cent.	49 per cent.
	Controls (40)	58 ,, ,,	37 ,, ,,
	Rheumatics and controls (79)	62 ,, ,,	43 ,, ,,
Group giving weakly positive reactions to H.S.E. (12-20 mm.)	Rheumatics (11)	33 ,, ,,	11 ,, ,,
	Controls (17)	35 ,, ,,	41 ,, ,,
	Rheumatics and controls (21)	34 ,, ,,	26 ,, ,,
Group giving negative reaction to H.S.E.	Rheumatics (10)	20 ,, ,,	20 ,, ,,
	Controls (23)	13 ,, ,,	14 ,, ,,
	Rheumatics and controls (33)	17 ,, ,,	17 ,, ,,

This association may be due to the presence of a protein constituent common to hæmolytic and non-hæmolytic streptococci as shown by Lancefield (1928).

Age and the allergic skin reaction to H.S.E.—Collis (1932) recorded the interesting fact that in his series the age period 12–14 was that of maximum sensitivity and that no increase in incidence of reactors was observed in higher age periods. Derick and Fulton (1931) after a study of cutaneous reactions to a purified hæmolytic streptococcus nucleo-protein preparation in 670 cases also noted 15 years as the age up to which the proportion of positive reactors increased. They stated after 15, age played no part in determining the presence or absence of sensitiveness. Table 7 summarizes our results as they relate to this question. Features of the table are the high incidence of reactions (90 per cent.) in the age period 10–15 years with

the fall to 68 per cent. in the over 15 group: also the curve of controls follows the same lines as that of cases in that no rise occurs over 15 years. The viridans and ' gamma ' extract reactions also show the same fall after the 10–15 age-group. Collis (1932) recorded that if the figures were corrected to allow for the interval since the last acute attack, the differences referable to age itself were slight. We have not sufficient data to give any opinion on this point except to state that our ' over 15 ' group was largely composed of adult patients in a general hospital, all being under treatment for a primary attack or recurrence of the disease. It would appear, therefore, that even in presence of active disease the age group including adult patients yields a smaller proportion of reactors than the age group 10–15.

TABLE 7.

AGE FACTOR INFLUENCING SKIN REACTIONS TO EXTRACTS OF STREPTOCOCCI OF DIFFERENT TYPES. BASED ON A SERIES OF 77 CONSECUTIVE RHEUMATIC CASES AND 88 CONTROLS.

Streptococcus extract	Groups	Percentage positive* reactions in 3 age groups		
		5–9 yr.	10–15 yr.	Over 15 yr.
Hæmolytic	Rheumatic	46	90	68
	Control	35	66	66
Viridans	Rheumatic	56	61	46
	Control	40	43	19
' Gamma '	Rheumatic	19	56	38
	Control	37	34	25

* Strong reactions only are included. When weak positive reactions are added the relative incidence as between one age group and another is maintained. The number in each group on which the above percentages are based ranged from 21 to 43 cases or controls.

Not only the proportion of reactors but also the severity of reactions was greater at the age period 10–15 years. This could be demonstrated by taking the mean of the diameters of all reactions to H.S.E. in each age group (see Table 8). This table shows the surprising fact that in the age group 5–9 years the average diameter of reactions in controls is exactly equal to that in rheumatic cases.

TABLE 8.

MEAN DIAMETER OF REACTIONS TO H.S.E. IN RHEUMATIC AND CONTROL GROUPS AT THREE AGE PERIODS.

Group	5–9 years		10–15 years		Over 15 years	
	Total	Mean diameter	Total	Mean diameter	Total	Mean diameter
Rheumatic	22	18·18 mm.	21	35·90 mm.	31	21·58 mm.
Controls	38	18·18 mm.	20	30·20 mm.	21	20·33 mm.

Clinical type of rheumatism and its relation to the results of skin reactions.—Three convenient clinical subdivisions were used for the classification of the cases of our rheumatic series. A febrile group was composed of those showing fever at the time of the test or during the preceding four weeks. The afebrile group were those cases of carditis more definitely subacute or chronic who had been afebrile for at least one month before the test. The cases of chorea constituted the third group.

Table 9 records the results. The following facts were noteworthy: (1) only the H.S.E. reaction appeared to be influenced to any marked extent by the clinical type of disease; (2) the febrile cases showed approximately only half the incidence of positives found in the chorea group (90 per cent.); (3) the afebrile group occupied a position midway between the febrile and chorea groups.

TABLE 9.

INCIDENCE OF SKIN REACTIONS TO EXTRACTS OF HÆMOLYTIC, VIRIDANS AND 'GAMMA' TYPE STREPTOCOCCI IN RELATION TO CLINICAL TYPE OF THE DISEASE. FEBRILE—PYREXIA PRESENT AT TIME OF TEST OR DURING PRECEDING FOUR WEEKS. AFEBRILE—NO PYREXIA WITHIN FOUR WEEKS BEFORE TEST.

Clinical type	Reaction to extract of hæmolytic strep.				Reaction to extract of viridans strep.				Reaction to extract of 'Gamma' strep.			
	Total	+	±	—	Total	+	±	—	Total	+	±	—
Febrile	28	13	7	8	20	8	4	8	20	7	3	10
per cent.		47		29		40		40		35		50
Afebrile	33	24	4	5	28	17	5	6	28	11	6	11
per cent.		73		15		61		21		39		39
Chorea	19	17	1	1	15	7	5	3	15	5	3	7
per cent.		90		5		47		20		33		47

\+ signifies skin reaction of 20 mm. mean diameter or more.
± ,, ,, ,, ,, 12–19 mm. mean diameter.
— ,, ,, ,, ,, less than 12 mm. mean diameter.

An analysis of the influence of the time elapsing between the onset of illness and the test upon the sensitivity to the hæmolytic streptococcus extract showed that as this time interval increased so did the percentage of positive reactors (Table 10). This, however, appeared to be almost entirely due to the fact that the percentage of febrile cases decreased as the time interval lengthened. It was found impossible to show any direct relationship between the number of recurrences and the skin reactions,

TABLE 10.

INTERVAL BETWEEN ONSET OF RHEUMATIC INFECTION AND TIME OF SKIN TEST, AS INFLUENCING TYPE OF REACTION TO HÆMOLYTIC STREPTOCOCCUS EXTRACT.

	Less than 1 month	1–3 months	4–6 months	Over 6 months
Total cases	18	16	10	15
Strong positive	9=50%	7=65%	7=70%	14=93%
Weak positive	3=17%	4=16%	2=30%	none
Negative	6=33%	5=19%	1=10%	1=7%

SORE THROATS. Of 66 cases, 31 gave a history of sore throats. In 16 cases a history was obtained of the date of the last attack, and of these 3 had had an attack of tonsillitis 2–3 weeks before the onset of rheumatic pains, and 2 of them had attacks after admission to hospital. Table 11 shows that a larger number of those with a history of tonsillitis gave a positive reaction to the hæmolytic streptococcus extract than those with no such history.

TABLE 11.

SHOWING RELATION BETWEEN OCCURRENCE OF SORE THROAT AND TYPE OF REACTION TO HÆMOLYTIC STREPTOCOCCUS EXTRACT.

	No. of cases	Strong positive	Weak Positive	Negative
History of sore throat	31	20=65%	7=22%	4=13%
No history of sore throat	35	17=49%	9=25·5%	9=25·5%

TONSILLECTOMY. Of the 74 cases of which clinical notes are obtainable, 11 had had the tonsils removed, in 2 cases the operation being performed after the skin tests had been carried out. Of the remaining 9, 7 gave positive skin reactions, and 2 a weakly positive reaction. Two of these cases underwent the operation after admission to hospital, one 25 days, and the other 26 days before the skin tests were carried out, and both gave strongly positive reactions.

SCARLET FEVER. Of 63 cases, 9 (11 per cent.) had had scarlet fever; of these, 3 gave positive, 4 weakly positive and 2 negative reactions.

Dick reaction in acute rheumatism.—The Dick test was performed on every case of rheumatism and every control. Table 12 records the results, showing that the incidence of positives (16 per cent.) was unduly low in the rheumatic group. The finding of 28 per cent. as the Dick positive rate in controls is more normal. In an attempt to estimate how far a previous infection with hæmolytic streptococci has been operative in the causation of acute rheumatism the Dick test would appear to be a valuable guide. The presence of a positive Dick reaction does not however preclude the possibility of a previous infection with hæmolytic streptococci.

TABLE 12.

RESULTS OF DICK TEST CARRIED OUT ON 142 CASES OF ACUTE RHEUMATISM AND 141 CONTROLS.

Group	Total	Positive		Negative	
		Total	Percentage	Total	Percentage
Rheumatic	142	23	16	119	84
Control	141	40	28	101	72

Throat swab examinations.—Investigation of the throat yielded hæmolytic streptococci in 46 out of 107 rheumatic cases, and in 23 out of 116 controls. The percentages of individuals harbouring these micro-organisms are thus 43 and 20 respectively. The micro-organisms are being maintained and studied further, especially with a view to determining whether any serological relationships can be demonstrated.

Table 13 and Table 14 show the results in an attempt to ascertain whether the finding of hæmolytic streptococci in the throat could be correlated in any way with the results of streptococcus extract and Dick reactions. It was thought possible that those in the rheumatic group, in the presence of the micro-organism, might have shown more tendency to develop the allergic reaction than the controls. This was not so, 83 per cent. of rheumatics and 95 per cent. of controls being positive to H.S.E. in presence of the hæmolytic streptococci (Table 13). Again, where hæmolytic streptococci were not isolated the results were very similar in the two groups.

TABLE 13.

CORRELATION OF RESULTS OF SKIN REACTIONS TO EXTRACT OF HÆMOLYTIC STREPTOCOCCUS WITH THE FINDING OF THAT MICRO-ORGANISM IN THE THROAT SWAB.

Group	Total cases	Hæmolytic streptococcus isolated in	Percentage giving positive H.S.E. skin reaction*	
			Positive swab	Negative swab
Rheumatic	77	52	83	81
Control	81	25	95	71

* All reactions over 12 mm. diameter are included.

The same facts in relation to the Dick test are given in Table 14. Again no significant differences in Dick reactivity are associated with the finding of hæmolytic streptococci in the throat. The table shows the rather striking fact that 22 per cent. and 15 per cent. of cases and controls respectively were Dick-positive while carrying a hæmolytic streptococcus in the throat.

TABLE 14.

CORRELATION OF RESULTS OF DICK REACTION WITH THE FINDING OF HÆMOLYTIC STREPTOCOCCI IN THE THROAT SWAB.

Group	Total cases	Percentage in which hæmolytic streptococci isolated	Percentage Dick positive	
			Positive swab	Negative swab
Rheumatic	75	48	22	31
Control	82	24	15	19

Absence of toxigenicity, or low invasive powers of the micro-organism, or alternatively a high tissue resistance of the patient, might readily account for these results.

Discussion.

Our work does not add much support to the allergic theory of acute rheumatism. At the outset we are faced by two sets of phenomena which may or may not be associated:—(1) Those referable to infection with the hæmolytic streptococcus which may quite well exist without any symptoms of acute rheumatism. Among these may be placed the finding of hæmolytic streptococci in the throat before or during an attack, the allergic reaction (shown by Gibson and McGibbon (1932) to develop in a high proportion of cases of non-rheumatic hæmolytic streptococcal infection, e.g., scarlet fever), the tendency towards a Dick-negative state and the presence of anti-streptolysin in the serum as shown by Todd (1932). These may occur in the absence of any suggestion of rheumatism, and one or more are probably inseparably associated with all hæmolytic streptococcal infection. (2) Those referable to acute rheumatism, polyarthritis, carditis, chorea, etc.

Evidence associating the infection with the rheumatic state is to be found in the observation of epidemic rheumatic relapse superimposed on throat infection with hæmolytic streptococci. In assessing the value of the present work it must be borne in mind that no claim has ever been made for the H.S.E. skin reaction as specific in acute rheumatism. It is at most an index of previous infection with hæmolytic streptococci.

In our series the incidence of positive reactions among rheumatic cases was similar to that reported by Collis (1932), but in controls the incidence was much higher than in his series. Our early controls were out-patients and patients in medical wards of children's hospitals: these gave figures of the same order as Collis'. Later we gained access to cases (and controls) in an institution in which many patients were convalescent after ear, nose and throat operations. Controls were selected quite impartially from among

patients presenting no suggestion of rheumatism. A very high proportion of these latter controls reacted, many with some severity. At first we thought that these cases, probably infected with hæmolytic streptococci, should not be used, but it was then realized that to exclude all those with a recent history of hæmolytic streptococcal infection would render the control series quite valueless. Especially would this be the case in view of the probability of transmission from case to control and vice versa within the same ward.

Our results may be summed up by stating that cases of rheumatism revealed rather more evidence of previous infection with the hæmolytic streptococcus than did non-rheumatic controls. The paramount question of what peculiarity exists in the micro-organism or the host to determine acute rheumatism as the resultant of streptococcal infection remains unanswered. The question of why some cases of gonococcal infection have joint involvement, while others have not, appears to be analogous; and in the present state of our knowledge of the interaction of host and micro-organism no explanation is available.

The finding of hæmolytic streptococci in the throats of twice as many cases as controls was of interest. The strains are being further studied. So far we have ample evidence that the micro-organisms isolated are serologically heterogeneous. By a serological study of the strains from cases and controls, obtained simultaneously in the same wards, it will be possible to throw light on the precise significance of the micro-organisms in relation to the disease, since the hæmolytic streptococcus strains recovered from rheumatic fever throats may be simply chance infections subsequent to the onset of the disease and entry into hospital. The finding of the micro-organism in a higher proportion of cases than controls may mean no more than that the throat in acute rheumatism is a more favourable nidus for its persistence.

Clinically the two main features were the large percentage of positive skin reactions to H.S.E. among the cases of chorea (90 per cent.), and the comparatively small number of such reactions among the febrile group (Table 9). That this predominance of positive reactions in the chorea group was to a certain degree selective, and not merely an increased reactivity to foreign proteins in general, was shown by the reactions to the streptococcus viridans and the ' gamma ' streptococcus extracts which were less than those in the other two groups.

As an aid to diagnosis or prognosis the skin reactions were of little, if any, value. Because one patient gave a strong reaction, while another only a weak one, it was not possible to say either that the prognosis was worse in the one case than in the other, or even that one was a case of rheumatism and the other was not. The only modifying factor in either group was apparently the presence or otherwise of pyrexia and, if present, its duration.

One of the most interesting results of our study has been from the group of rheumatic and control cases which was investigated at the large convalescent hospital mentioned. Here we were able to observe a number of patients with quiescent rheumatism, all showing an intense allergic reaction, in whose throats hæmolytic streptococci were abundant. Such cases

appeared to provide all the conditions necessary for relapse, and yet none occurred. It was noteworthy also that in this institution the controls showed more marked allergy than the rheumatic cases elsewhere.

These results suggest strongly that the allergic skin-reaction is an index of the hæmolytic streptococcus factor alone. Infection with this micro-organism may be an important factor in the production of the rheumatic state but the intradermal test of allergy is not an indicator of the reactive state in the patient necessary to produce the ' rheumatic ' response to such infection.

At the same time our findings adduce no evidence which is contrary to the theory of hæmolytic streptococci as the cause of acute rheumatism. Thus we find that 25 per cent. of cases do not show skin hypersensitiveness to the endo-products of the organism, a finding to which Gibson and McGibbon (1932) showed a parallel after scarlet fever, a disease known to be due to this micro-organism. Again, a high percentage of positive reactions among controls, varying with environment as shown by our Astley Ainslie Institution cases, also means little when the high risk of infection of all with the streptococcus is taken into account. The finding of positive Dick reactions among rheumatics is also of little import, and in no way rules out the possibility of a previous infection with the micro-organism. Apart from the existence of atoxigenic strains it must be remembered that a persistently positive Dick reaction is frequently found even after scarlet fever.

Epidemiological and clinical evidence is strongly in favour of an association between the hæmolytic streptococcus and acute rheumatism. In the absence of a susceptible animal all work must approach the subject indirectly. The presence of cutaneous hypersensitiveness is probably not the crucial index of the reactive state in the patient necessary to produce rheumatism after infection.

Summary.

1. The intradermal reactions to extract preparations of streptococci of different types have been ascertained.

2. Strongly positive reactions to extract of hæmolytic streptococcus are more common in rheumatic than in control cases.

3. Reactions to viridans and ' gamma ' streptococcus extracts show no significant difference as between rheumatic and control series. There is, however, some evidence that the incidence of reactions to extracts of non-hæmolytic streptococci is associated with the degree of sensitivity to antigens of hæmolytic strains.

4. The Dick reaction was positive in 16 per cent. of rheumatic cases as compared with 28 per cent. of controls. Hæmolytic streptococci were isolated from the throats of 43 per cent. of rheumatic cases as compared with 20 per cent. of controls. In neither rheumatic nor control groups could any significant differences in skin reactivity be made out between those who harboured the micro-organisms and those who did not.

5. The highest proportion of positive skin reactions to the extract of hæmolytic streptococcus was found in cases of chorea. Afebrile cases were

less hypersensitive, and febrile cases (including those in whom fever had been present within one month preceding the test) were least sensitive.

6. Of 66 cases in which a reliable record could be obtained, 31 gave a history of sore throats, but only 3 cases had had an attack of tonsillitis within two or three weeks of admission to hospital.

7. Our results were in agreement with those of previous workers who have shown that skin sensitiveness increases with age up to 15 years, after which no further increase is noted.

8. The conclusion is reached that the allergic skin reaction may be a result of previous infection with hæmolytic streptococci. The presence of skin hypersensitiveness to intracellular antigens of this micro-organism cannot be regarded as an indication of the special reactivity necessary to produce acute rheumatism on infection.

9. The intradermal reaction does not appear to be of direct diagnostic or prognostic value in cases of rheumatic infection.

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REFERENCES.

Birkhaug, K. E., *J. Inf. Dis.*, Chicago, 1927, XL, 549.
Coburn, A. F., *The Factor of Infection in the Rheumatic State*, Baltimore, 1931.
Collis, W. R. F., *Lancet*, Lond., 1931, i, 1341.
Collis, W. R. F., & Gray Hill, N., *Quarter J. Med.*, Oxford, 1932, N.S., I, 511.
Collis, W. R. F., & Sheldon, W., *Lancet*, Lond., 1932, ii, 1261.
Derick, C. L., & Fulton, M. N., *J. Clin. Invest.*, Baltimore, 1931, X, 121.
Gibson, H. J., & McGibbon, J. P., *Lancet*, Lond., 1932, ii, 729.
Glover, J. A., *Ibid.*, 1930, i, 499.
Irvine-Jones, E., *Arch. Int. Med.*, Chicago, 1928, XLII, 784.
Kaiser, A. D., *J. Inf. Dis.*, Chicago, 1928, XLII, 25.
Lancefield, R. C., *J. Exp. Med.*, N.Y., 1928, XLVII, 469, 481.
Mackenzie, G. M., & Hanger, F. M., Jr., *J. Immunol.*, Baltimore, 1927, XIII, 41.
Nicholls, E. E., & Stainsby, W. J., *J. Clin. Invest.*, Baltimore, 1931, X, 337.
Schlesinger, B., *Arch. Dis. Child.*, Lond., 1930, V, 411.
Sheldon, W., *Lancet*, Lond., 1931, i, 1337.
Swift, H. E., Wilson, M., & Todd, E. W., *Amer. J. Dis. Child.*, Chicago, 1929, XXXVII, 98.
Todd, E. W., *Brit. J. Exp. Path.*, Lond., 1932, XIII, 248.

RENAL RICKETS FOLLOWING ACQUIRED NEPHRITIS

BY

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In the previous number of the 'Archives of Disease in Childhood,' E. A. Cockayne and F. P. Lee Lander[1], under the title of 'rickets following an attack of acute nephritis,' recorded a case in which the bony changes of renal rickets had supervened in a previously healthy child who had contracted a severe nephritis. In their comments they remarked on the fact that medical literature contained hardly any reference to this type of case.

Their communication has prompted me to report the following two cases which appear to be of the same type as their own.

Case reports.

Case 1.—William H., aged 17 years. In July, 1922, he was admitted to a fever hospital with acute nephritis. There was a history of a scarlatiniform rash a short time previously. While in hospital his albuminuria diminished considerably but had not completely disappeared at the time of his discharge.

His mother states that up to the time of this illness he was quite normal, but that since then his growth has been much retarded.

He was first diagnosed as a case of renal rickets in 1928, and in the following year his blood urea measured 140 mgrm. per cent. At the present time, aged 17 years, he has the stature and appearance of a boy of 9 or 10 years. He is in fair health, but he has severe genu valgum. He shows typical radiological evidence of renal rickets.

Case 2.—Olive P., aged 14 years. In 1925 at the age of 7 years she had scarlet fever and nephritis. Since that time, according to her mother, she has been very backward. In July, 1931, her blood urea was 115 mgrm. per cent.; blood calcium 7 mgrm., and blood phosphate 6 mgrm. In April, 1932, she was admitted to hospital with a history of 1 year's increasing genu valgum. The X-ray appearances were typical of renal rickets.

Discussion.

Renal rickets is usually described as a disease associated with congenital changes in the kidneys. Most commonly the kidneys have the appearance of chronic interstitial nephritis (Ashcroft[2]), although Brockman[3] has met an instance with typical deformities associated with congenital cystic kidneys.

As regards the possible development of renal rickets as a sequel to an acquired acute nephritis it must necessarily be a matter of great difficulty to prove in any individual case that the kidneys were healthy until the onset of the acquired disease. Although deformities and stunted growth may not be noticed until after the acute attack this is not necessarily sufficient

proof. It may be that the acute nephritis has occurred in kidneys already diseased and so unmasked or hastened the onset of the symptoms of renal rickets. It is not so uncommon for cases of renal rickets to give a history of acute nephritis, and the difficulty of assessing accurately the value of the clinical history is enhanced by the fact that cases of renal rickets do not find their way to the orthopædic surgeon much before the age of ten years.

In the case reported by Cockayne and Lander there is one point which strongly supports their contention that there was no congenital disease of the kidneys: namely, that the symptoms in the chronic stages of the acquired nephritis were of the hydræmic type. Their long observation of the case and the conditions found post mortem also support their view. Barber[4] describes an interesting case (No. 7 in his series). The child had a history of diabetes insipidus at the age of three years, but although the urine was examined many times, no albuminuria was ever found. After an attack of scarlet fever the child developed deformities and albuminuria. It does not seem possible to exclude the presence of renal disease in early life on this history.

Many orthopædic surgeons would readily allow that renal rickets may follow acquired nephritis or even chronic pyelo-nephritis; but owing presumably to the difficulty in the production of satisfactory proofs, there is little reference to such cases in the literature.

REFERENCES.

1. Cockayne, E. A., & Lander, F. P. L., *Arch. Dis. Childh.*, Lond., 1932, VII, 321.
2. Ashcroft, G. V., *J. Bone & Joint Surg.*, Boston, 1926, VIII, 279.
3. Brockman, E. P., *Brit. J. Surg.*, Bristol, 1927, XIV, 634.
4. Barber, H., *Quart. J. Med.*, Oxford, 1921, XIV, 205.

A REVIEW OF THE USE OF IMMUNE SERUM IN ACUTE POLIOMYELITIS

BY

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Poliomyelitis is an acute infection of the central nervous system, with an incubation period of from 7 to 14 days, and its highest incidence in the summer and early autumn (July to October). It is characterized by an abrupt onset with fever and marked constitutional and nervous symptoms: these develop rapidly and rarely last more than a few days. Although this is usually termed the pre-paralytic stage, it is, in actual fact, the active period of the disease. These symptoms terminate quite abruptly with the appearance of the paralysis. Then, in reality, the disease is over, and treatment from this stage onwards is of a passive character (Ayer[3]).

Active measures, therefore, to be of any value must be instituted prior to the development of the paralysis, and this is the aim and object of treatment by means of ' convalescent serum.'

During the last several years a large amount of work has been carried out, particularly in America and Australia, and there have been innumerable publications on the use of convalescent serum in the treatment of poliomyelitis. It is instructive, therefore, to review briefly this large mass of work and to attempt to assess the value of this line of treatment.

All writers emphasize the fact that the cases must be diagnosed and treated in the pre-paralytic stage if beneficial results are to be obtained. Poliomyelitis is due to a true filtrable virus, and no disease due to a filtrable virus is known to be benefited by an antiserum after clinical symptoms have developed (Park[15]). Unfavourable opinion of serum therapy has been created by delay and consequent unsuccessful administration in the presence of paralysis. At such a stage it is wasteful and futile to inject serum. Unless this fact is constantly borne in mind there is real danger that a most valuable therapeutic advance may fall into disrepute.

The pre-paralytic stage.—An essential criterion, therefore, for successful serum therapy is the diagnosis of poliomyelitis in its acute, or so-called pre-paralytic, stage. This stage presents a definite chain of symptoms and physical signs which can be recognized. In many cases, particularly in the presence of an epidemic, it is possible to be reasonably certain of the diagnosis on clinical grounds alone, but the diagnosis should never be made and serum treatment should never be instituted until the cerebro-spinal fluid has been examined.

Under these circumstances too much insistence cannot be placed on early diagnosis and the manifestations of the acute phase are worthy of consideration in detail. This acute phase usually lasts from 24 to 48 hours. The most typical early and constant symptom is fever, and though this is rarely above 102° the child is more prostrate than the temperature would indicate. Severe headache, pains in the neck, back and elsewhere, one or two attacks of vomiting, apathy, indifference and drowsiness are other common symptoms. The child may appear to be irritable when roused, but careful examination will reveal that this is really due to hyperæsthesia and muscular rigidity.

Of physical signs the most important is rigidity of the neck muscles. This is rarely so severe as to cause definite head retraction, and in fact may not be evident unless specifically searched for. In passing it is interesting to record that the importance of this sign was recognized by one of the earliest describers of the disease, namely Medin; and in fact even to-day poliomyelitis is popularly called the ' neck disease ' in Sweden. This rigidity of the neck muscles has received various designations, and may be elicited in various ways. If the child is not too ill to co-operate in the examination he may be asked to pick up a penny from the floor or to kiss his knee. A willing child will attempt the necessary movement but will fail to complete it on account of pain or discomfort. Again, when the child is placed in the sitting position, the hands are placed behind the body to support it (Amoss's sign). Another test is to ask the child to touch his sternum with his chin (the chin sign); a child in the pre-paralytic period will try to do this by opening the mouth. What these various tests reveal is the unwillingness of the child to flex the spine. Other physical signs are a rapid pulse rate, out of all proportion to the temperature. There may also be fine tremor of the hands and lips, and the deep reflexes are often increased in the early stages. Constipation is the rule. Retention of urine, photophobia, and sweating of the face and neck are less commonly observed. Some authors (Ayer[3]) say that coma and convulsions do not occur; but others (MacNamara and Morgan[13]), whilst admitting that they may occur, qualify this by stating that repeated convulsions suggest another diagnosis.

It is obvious from this description that on clinical grounds alone the differential diagnosis must frequently be a matter of great difficulty and often impossible. The important point, however, is that if the clinical picture in any way suggests the diagnosis of acute poliomyelitis, lumbar puncture must be performed and the cerebro-spinal fluid examined both cytologically and biochemically.

The cerebro-spinal fluid usually flows out under a slightly increased pressure, it is clear unless the cell content is very high, when a slight haziness may be discernible. The cytology of the fluid is of great diagnostic importance. Most cases of poliomyelitis show a cell count between 50 and 200, but counts up to 700 have been recorded. The count may be affected by the severity of the infection and the time of lumbar puncture. The types of cell present have been found to be different by different observers, in, it

should be added, different epidemics. Thus, MacNamara and Morgan[13] state that early in the pre-paralytic stage the polymorphonuclear cells are increased, but they disappear as the lymphocytes increase until, at the stage of paralysis, only 5 to 10 per cent. of the cells are polymorphonuclears. Thelander, Shaw and Limper[18], on the other hand, found that the average percentage of polymorphonuclear cells in the fluid in the first five days of the disease was about 50 per cent. and that their percentage was independent of the day of the disease. They appreciate that their findings are not in accordance with those of most authors, and suggest that this may be accounted for by variations in different epidemics and by the technique of staining and studying the cells.

It is evident from these results, therefore, that in some cases at any rate the differential diagnosis, particularly between poliomyelitis and tuberculous meningitis, may be impossible by cytological examination alone. Consequently, the necessity for biochemical examination becomes obvious. The protein content of the fluid is increased in both these diseases, so again for differential diagnosis this observation is of no value. Estimation of the chloride content, however, is of very considerable importance. In poliomyelitis the chloride content of the cerebro-spinal fluid is not disturbed (730 mgrm. per cent.). In the vast majority of cases of tuberculous meningitis, on the other hand, the chlorides are appreciably reduced. It is true that occasionally a normal or even high chloride content may be found in tuberculous meningitis (Neale and Esslemont[14]), but as this occurs late in the disease there is no real likelihood of confusion.

To recapitulate briefly, the characteristic findings in the cerebro-spinal fluid are (1) an increased cell content; (2) normal chloride content, and (3) increased protein; and as Gordon[7] has expressed it, the diagnosis of pre-paralytic poliomyelitis consists of a healthy clinical suspicion and a lumbar puncture.

Immune serum.

The employment of convalescent human serum in the early treatment of poliomyelitis is founded upon sound experimental evidence in monkeys. Flexner and Lewis[1] (1910) were the pioneers in this field and during the next few years their results were confirmed by other observers. These investigators showed that if the virus of poliomyelitis was mixed with convalescent serum and injected into monkeys, no paralysis developed[16]. Further, monkeys inoculated with the virus intra-cerebrally or intra-nasally could be protected from developing the paralytic stage by the intra-spinal injection of convalescent serum, even if the serum was injected as long as 18 to 24 hours after the virus. It is important to note that these workers found that equally satisfactory results could be obtained with either convalescent monkey or convalescent human serum, but that normal (i.e., non-immune) monkey and normal human serum was without any appreciable effect[15],

These experiments, then, form the basis for the use of convalescent serum therapeutically in man.

The serum of a person who has had poliomyelitis has been demonstrated to possess high viricidal properties for many years afterwards. In fact, from the few experiments that have been conducted, the lapse of time would not appear to reduce its potency to any appreciable extent, Moreover, there is some evidence that individuals belonging to blood-group 2 are, on average, more resistant to poliomyelitis than those of other groups and their serum has proved, in a few instances, to be more effective in neutralization tests, than serum from donors of other groups[17]. From the published evidence it seems wise to wait some months after the attack of poliomyelitis before using the blood of that patient for therapeutic purposes, but the best time to collect the serum has not yet been ascertained. It is true that the blood of some people who have not had the disease clinically also possesses neutralizing properties, which may be the result of an abortive and unrecognized attack, or from repeated sub-minimal infections in childhood, but this cannot be depended upon without testing. Such testing necessitates carefully controlled animal experiments and until this can be carried out on a wide scale it is best to use only serum from known clinical cases, at any rate for curative purposes.

As the severity of the original infection bears no known relationship to the subsequent viricidal concentration of the serum, the blood of mild cases can, in the present state of knowledge, be regarded as equally efficacious as that from even the most severe cases. There is one other important point in this connexion; it is now known that there are several varieties of poliomyelitis virus, so it is wise to use pooled serum from different cases and from different epidemics if the most satisfactory results are to be achieved.

Preparation of serum.—In the preparation of the serum MacNamara and Morgan[13] advise that no antiseptic be added, as they consider that this may be the cause of certain unfavourable reactions that have been noted after the injection of the serum. In America, on the other hand, some antiseptic is usually added. Such serum, carefully prepared, has been stored for over three years without evident deterioration of its potency.

Methods of administration and dosage of serum.—The diagnosis of the pre-paralytic stage having been established, the injection of immune serum is a matter of extreme urgency. The treatment is a true medical emergency. In actual practice it is preferable to perform lumbar puncture, withdraw a few cubic centimetres of fluid and leave the needle in situ while the fluid is being examined. If the diagnosis is confirmed, serum may then be administered intrathecally without delay, and the patient is saved the discomfort of a second puncture. Coincident with this intrathecal injection serum should also be given intravenously.

It must be remembered that the aim of treatment with convalescent serum is to produce a passive immunity. The initial dose, therefore, should be high, the amount depending not on the age of the patient but rather on

the duration and severity of the symptoms. Intrathecally the amount injected should be slightly less than the quantity of cerebro-spinal fluid withdrawn. An intravenous injection is equally effective, but there must be a certain delay in it reaching the central nervous system, and time is a matter of considerable importance.

The total initial dose of serum, i.e., intrathecally and intravenously, recommended varies from about 25 to 100 c.cm., and if there is no improvement in 18 to 24 hours this dose should be repeated.

Results of serum therapy.—To analyze critically the published results of the serum treatment of poliomyelitis is no easy task. By no means all patients who contract this disease develop paralysis, and there must be an appreciable number of such in every series of published cases treated with serum. Another point to be remembered is that the physical signs and symptoms in the pre-paralytic stage do not give any indication of what the ultimate outcome will be (Aycock[1]); in other words, there is no relationship between the severity of the pre-paralytic symptoms and the extent of the ensuing paralysis. Further, in every series of serum-treated cases the question of accuracy of diagnosis arises.

Poliomyelitis varies in its virulence as do all epidemic diseases, so that extreme caution must be exercised in comparing results of treatment in different places at the same time, or in the same locality in different epidemics.

A brief epitome of a few of what seem to me the more important published papers will serve to define best the present position and opinions of serum therapy.

In 1928 Aycock and Luther[2] published the results of the treatment during the first 4 days of the disease of 106 children in whom paralysis had not appeared. The serum was administered intrathecally and intravenously. One child died and 64 per cent. of the remainder developed some paralysis, but the average total paralysis in the serum-treated cases was very considerably lower than in 483 untreated cases reported in the same year. In fact, only 5·7 per cent. of the treated cases developed severe paralysis, in comparison with 46 per cent. of the untreated ones. These authors concluded that the administration of convalescent serum in the pre-paralytic state exercised a favourable effect on the subsequent course of the disease.

Kellog[9], in 1929, critically analyzed what he considered to be the more important published results. His conclusions were that convalescent serum was of value in the treatment of poliomyelitis, and that its use should be encouraged and extended.

Early last year (1932) a most important and instructive paper was published by Kramer and Aycock[11]. They endeavoured to test the results of serum therapy by way of a controlled experiment and failed to obtain statistical evidence that convalescent serum produced any appreciable effect. There was no evidence to show that the serum was of no value, and they considered that there is justification for its employment on a larger scale.

In 1931 in the State of New York 1,019 cases of poliomyelitis were diagnosed in the pre-paralytic stage (Park[16]); 572 were treated with serum and the remainder received no serum, yet there was no appreciable difference in the results of the two groups. Nevertheless, the opinion was expressed that serum should continue to be used.

In Australia, MacNamara and Morgan[13] have been studying this problem for some years. In their hands the use of human immune serum, administered in the pre-paralytic stage, has given excellent results, as evidenced by a low mortality rate, a low average total paralysis and a strikingly low proportion of paralysis of the severer grades. They further state that if ample serum is available its administration within 24 hours of the development of paralysis to a febrile patient is justified, and is usually followed by a fall of temperature and arrest of paralysis. If given later, when paralysis is stationary, serum is of no value.

Whilst most writers on this subject are guarded in expressing their conclusions on statistical evidence, the impression is gained from reading their papers that those who had most experience with serum do feel that a strong case has been made out for its employment and ample justification exists for its continued and extended use.

To the punctilious statistician ruthless alternation of cases would be the only way of obtaining conclusive information. But, as is so well put by Kellog[9], a physician dealing with the lives of children instead of guinea-pigs naturally shrinks from such a procedure if he has any confidence at all in the treatment under investigation.

Prior to the introduction of immune serum, the study of poliomyelitis in its pre-paralytic stage received scant attention. With the advent of serum therapy, however, great impetus was given to the study of the acute manifestations with the result that much further knowledge has been gained. In this connexion it has been suggested that the term ' infantile paralysis ' is misleading, as paralysis is an incidental and not an essential result of the infection. It is now beginning to be realized that poliomyelitis has a much greater incidence than has been appreciated in the past. For instance, in every epidemic it is now appreciated that there is no inconsiderable number of abortive and non-paralytic cases, which has been assessed as high as 50 per cent. in some epidemics. Again, small epidemics of an acute febrile disorder of an influenza-like type, of short duration and with no sequelæ, have been recognized as epidemics of poliomyelitis. For example, Paul in 1931 (see Poliomyelitis[17], p. 178) found the poliomyelitis virus in 2 out of 12 cases of minor illness, which cases did not subsequently show any signs by which the diagnosis of poliomyelitis might be made.

It follows, therefore, that until poliomyelitis in all its clinical aspects has been completely elucidated, the value of immune serum, its uses and its limitations cannot possibly be estimated with scientific accuracy.

If further knowledge is to be gained immune serum must be used much more extensively, but care should be taken to ensure that it is only used in the right cases and at the right time.

Lumbar puncture.

The place of lumbar puncture in the treatment of pre-paralytic poliomyelitis is worth brief consideration for several reasons. This, again, is a subject about which different views are held in America and in Australia.

First of all, it has been proved experimentally that an intact choroid plexus offers an important barrier to the ingress of the virus to the brain and spinal cord. Conversely, anything which causes damage to the plexus by setting up what is commonly called an aseptic meningitis or meningismus (e.g., sterile horse serum) allows the virus to penetrate more readily.

MacNamara and Morgan[13] are not in favour of lumbar puncture. In several of their cases that failed to respond to serum treatment there was a delay between the withdrawal of a large quantity of cerebro-spinal fluid and the administration of serum. They suggest that the withdrawal of large quantities of fluid during the pre-paralytic stage may have actually determined involvement of the spinal cord. Gordon[7] also issues a warning against lumbar puncture, as he fears that it may initiate involvement of the central nervous system by enabling the virus to penetrate the choroid plexus more readily.

Contrary views, however, are expressed by most American workers. In the Report of the International Committee[17] many American physicians are quoted as being very definitely in favour of lumbar puncture, per se, as a therapeutic measure, in fact it is held to be extremely valuable. As is pointed out, the cerebro-spinal fluid is usually under increased pressure, consequently the relief of this pressure by lumbar puncture is a rational procedure. These authors all noted a marked improvement in symptoms which invariably followed the withdrawal of fluid, namely, the cessation of vomiting, diminution in the rigidity of the spinal muscles and abatement of the hyperæsthesia. Some even go so far as to say that the relief of pressure may exercise a favourable influence in preventing the development of the paralysis or at least in modifying its progress.

Neither the Australians nor the Americans state how much fluid should be withdrawn. It should be noted, however, that MacNamara and Morgan[13] refer to the withdrawal of large quantities of fluid, which quite conceivably could do harm by damaging the choroid plexus. If, on the other hand, only sufficient fluid is allowed to escape to permit the pressure to return to normal, benefit and not harm may accrue. It is suggested that this may be the reason for the different opinions expressed.

Prophylactic treatment with immune serum.

Information on this point is meagre but important. The remarks of Miss Neal in the International Report[17] are both interesting and instructive. During an epidemic in Sweden in 1925, Davide inoculated 73 children with serum and only one, who had obviously been infected before the injection, developed the disease, which incidentally ran a mild course. Out of 84

that were not inoculated 14 developed poliomyelitis. In New York[16], in 1931, several hundred children received passive immunization and only 3 mild cases developed. In Bradford, U.S.A.[17], 1,300 children were inoculated with whole blood and none developed poliomyelitis, although 32 uninoculated children did contract the disease.

With regard to dosage, the Swedish children received 5 c.cm. of convalescent serum intramuscularly. The Americans advise 20 c.cm. of serum; or, if convalescent serum is not available, normal or adult serum or whole blood may be used in larger doses. A third method of passive immunization is that of utilizing refined immune horse serum. As this serum has a higher neutralizing power, 10 c.cm. intramuscularly is considered an adequate dose.

Passive immunization thus produced lasts not more than 3 weeks with human serum and about 2 weeks with horse serum. During an epidemic, therefore, repeated doses may be necessary. When using horse serum the possibility of serum sickness and hyper-sensitiveness must be borne in mind.

Thus evidence is accumulating to show that passive immunization against poliomyelitis is of value as a prophylactic measure, and has something to commend it. It seems unlikely that supplies of convalescent serum in this country will be available for this purpose for some time to come. Fortunately, it has been proved that in some parts of the world, at any rate, the serum of many adults is equal in neutralizing power to that of convalescent serum. For prophylactic purposes, therefore, in the presence of an epidemic nothing but benefit can accrue from the injection of adult serum or whole blood into known or suspected contacts. This should be adopted widely under carefully controlled conditions in order that its efficacy may be put to practical trial on an extensive scale and its value accurately assessed.

Summary and conclusions.

1. The diagnosis of poliomyelitis in its acute or pre-paralytic stage is an essential criterion for successful treatment by immune (convalescent) human serum.

2. This pre-paralytic stage presents a chain of symptoms and physical signs which can be recognized.

3. Lumbar puncture, with cytological and biochemical examination of the cerebro-spinal fluid, is necessary to establish the diagnosis and immune serum should not be administered until this has been done.

4. The employment of convalescent serum in the treatment of acute poliomyelitis is founded upon sound experimental data in animals.

5. The serum of a person who has had poliomyelitis has been demonstrated to possess high neutralizing properties for many years thereafter. Further, the blood of adults who have not suffered from the disease clinically may also possess neutralizing properties.

6. Whilst the statistical evidence in favour of immune serum is far from convincing, those who have had most experience with this form of treatment feel that a strong case has been made out for its employment and ample justification exists for its continued and extended use.

7. The place of lumbar puncture in the treatment of pre-paralytic poliomyelitis has not yet been settled. The withdrawal of sufficient fluid to allow the pressure to return to normal is probably of value in preventing the development of paralysis or at least in modifying its progress.

8. Evidence is accumulating to show that passive immunization against poliomyelitis may be of value as a prophylactic measure.

9. Much work yet remains to be done with regard to both the study of the acute disease as well as its treatment by immune serum before the many at present perplexing problems can be solved.

REFERENCES.

1. Aycock, W. L., *J. Am. Med. Ass.*, Chicago, 1932, XCIX, 1056.
2. Aycock, W. L., & Luther, E. H., *Ibid.*, 1928, XCI, 387.
3. Ayer, W. D., *Am. J. Med. Sc.*, Philad., 1929, CLXXVII, 540.
4. Flexner, S., & Lewis, A., *J. Am. Med Ass.*, Chicago, 1910, LIV, 1780.
5. Flexner, S., & Stewart, F. W., *Ibid.*, 1928, XCI, 383.
6. Flexner, S., & Stewart, F. W., *New Eng. Med. J.*, 1928, CXCIX, 213.
7. Gordon, J. E., *J. Am. Med. Ass.*, Chicago, 1932, XCIX, 1043.
8. John, R. L., *Am. J. Dis. Child.*, Chicago, 1931, XLII, 480.
9. Kellog, W. H., *J. Am. Med. Ass.*, Chicago, 1929, XCIII, 1927.
10. Kramer, S. D., *Ibid.*, 1932, XCIX, 1048.
11. Kramer, S. D., & Aycock, W. L., *New Eng. Med. J.*, 1932, CCVI, 432.
12. Levinson, S. O., McDougall, C., & Thalhimer, W., *J. Am. Med. Ass.*, Chicago, 1932, XCIX, 1058.
13. Macnamara, J., & Morgan, F. G., *Lancet*, Lond., 1932, i, 469.
14. Neale, A. V., & Esslemont, M. S., *Arch. Dis. Childh.*, Lond., 1928, III, 243.
15. Park, H. P., *J. Am. Med. Ass.*, Chicago, 1932, XCIX, 1050.
16. Park, W. H., *Lancet*, Lond., 1932, ii, 186.
17. *Poliomyelitis*, Rep. Internat. Com., Baltimore, 1932.
18. Thelander, H. E., Shaw, E. B., & Limper, M., *Am. J. Dis. Child.*, Chicago, 1931, XLII, 1117.
19. Silverman, A. C., *Ibid.*, 1931, XLI, 829.